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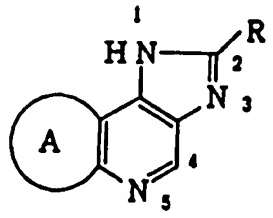
(54) Condensed imidazopyridine derivatives with psychotropic activity.

(57) A compound of the formula :



(I)

wherein R is an optionally substituted aryl group or an optionally substituted aromatic heterocycle group ; ring A is a 5 to 9 membered alicyclic group, in which one or more carbon atoms constituting said ring A may be replaced by O, S, SO, SO_2 and/or NR^1 (in which R^1 means hydrogen, alkyl, esterified carboxy group, carbamoyl or an acyl group) and/or said ring A may have an alkyl group as a substituent or its salt. The compounds of the present invention are useful as psychotropic agents such as antianxiety agents, anaesthesia antagonistic agents or cerebral function activators.

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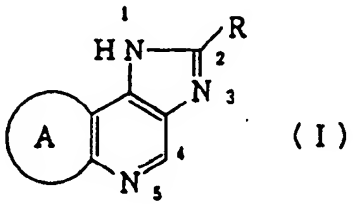
The present invention relates to novel condensed imidazopyridine derivatives having high affinity to benzodiazepine receptor, and, useful as psychotropic agents such as an antianxiety agent, anaesthesia antagonistic agent and cerebral function activator.

Benzodiazepine (BDZ) derivatives represented by diazepam have been used as an antianxiety agent for a long time. According to recent pharmacological studies, it has been found that a receptor showing an affinity specific to BDZ derivatives exists in the central nervous system. Then, as the result of extended studies, there have been developed BDZ agonists which are structurally different from BDZ but show high affinity to BDZ receptor and BDZ-like activity, BDZ inverse agonists which show high affinity to BDZ receptor but show a reversed action to BDZ, and BDZ antagonists which show high affinity to BDZ receptor but show no pharmacological activity and exhibit antagonistic action to the BDZ agonists or inverse agonists. On the other hand, various non-BDZ compounds are nowadays studied, and imidazopyridine derivatives disclosed in Japanese Patent Publication (Kokai) Sho 63-99069 and pyrazolopyridine derivatives disclosed in U.S. Pat. 4,826,854 and U.S. Pat. 4,740,512 are reported to show high affinity to BDZ receptor and useful as psychotropic agents.

However, said BDZ derivatives show sometimes various side effects such as dizziness and sleepiness. On the other hand, non-BDZ compounds nowadays under development also have drawbacks such as poor solubility and absorption. Accordingly, there has been a strong desire for development of novel non-BDZ compounds which are free of said drawbacks.

As the result of extensive study, the present inventors have found that compounds of the following formula (I):



(I)

wherein R represents an optionally substituted aryl group or an optionally substituted aromatic heterocyclic group; ring A represents a 5 to 9 membered alicyclic group, in which one or more carbon atoms constituting said ring A may be replaced by O, S, SO, SO_2 and/or NR^1 (in which R^1 means hydrogen, alkyl, alkoxycarbonyl, carbamoyl or an acyl group) and/or said ring A may have an alkyl group as a substituent, or its salt, can meet the above-mentioned requirements. The present invention is based on this finding.

The compounds of the present invention represented by the formula (I) exhibit agonistic activity, inverse agonistic activity, or antagonistic activity after binding to BDZ receptor. Those having agonistic activity are expected to be useful as sleep inducers or antianxiety agents, those having antagonistic activity useful as anaesthesia antagonists, and those having inverse agonistic activity useful as cerebral function activators.

In the present specification, the aryl group includes phenyl, naphthyl, anthryl and phenanthryl. These groups may have one or more substituents selected from alkyl, hydroxy, alkoxy, aryloxy, acyloxy (e.g. alkanoyloxy or aroyloxy), carboxy, ester (e.g. alkoxycarbonyl or aralkoxycarbonyl), cyano, amino, mono- or di-(substituted)amino, hydrazino, hydroxyamino, alkoxyamino, halogen, nitro, formyl, acyl (e.g. alkanoyl, aroyl), (thio)carbamoyl, (thio)carbomoyloxy, (thio) ureido, sulfonamide, mono- or di-(substituted)-sulfonamide, sulfonic acid, halogenoalkyl, hydroxyalkyl, alkoxyalkyl, acyloxyalkyl, nitroalkyl, (acyl)aminoalkyl, cyanoalkyl and carboxyalkyl. Preferred are phenyl optionally substituted by one or more substituents selected from methyl, methoxy and chlorine.

The aromatic heterocyclic group means a 5 to 6 membered carbon ring containing one or more atoms or groups selected from oxygen, sulfur and nitrogen atoms within the ring and may be optionally condensed with a carbon ring or other heterocyclic ring.

Examples of said aromatic heterocyclic rings are pyrrolyl, indolyl, carbazolyl, imidazolyl, pyrazolyl, benzimidazolyl, pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, cinnolyl, phthaladinyl, quinazolinyl, naphthylidinyl, quinoxalinyl, phenadinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, isoxazolyl, benzisoxazolyl, oxazolyl, benzoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, benzoxadiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, benzthiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, benzthiadiazolyl, furyl, benzfuryl, thienyl and benzthienyl. Further, these cyclic groups may optionally have one or more substituents selected from alkyl, hydroxy, alkoxy, carboxy, ester (e.g. alkoxycarbonyl and aralkoxycarbonyl), cyano, amino, mono- or di-(substituted)amino, hydrazino, hydroxyamino, alkoxyamino, halogen, nitro, formyl, acyl (e.g. alkanoyl and aroyl) (thio)carbamoyl, (thio)carbomoyloxy, (thio)ureido, sulfonamide, mono- or di-(substituted)sulfonamide, sulfonic acid, halogenoalkyl, hydroxyalkyl, al-

koxyalkyl, acyloxyalkyl, nitroalkyl, (acyl)aminoalkyl, cyanoalkyl and carboxyalkyl. Preferred are thienyl, furyl, isoxazolyl and pyridyl optionally substituted, for example, by methyl.

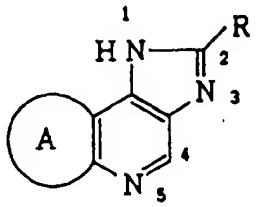
The 5 to 9 membered alicyclic group is condensed with the adjacent pyridine ring. Specific examples of the alicyclic group include a cyclopenteno ring, cyclohexeno ring, cyclohepteno ring, cyclooctено ring and cyclononeno ring, and a 5 to 7 membered alicyclic ring is preferred. Further, one or more of carbon atoms constituting said alicyclic ring may be replaced by O, S, SO, SO_2 and/or NR^1 (in which R^1 has the same significance as defined above). Such an alicyclic ring containing hetero atoms includes pyrrolidino, pyrrolino, imidazolidino, imidazolino, pyrazolidino, dihydrothiopheno, dihydrofurano, thiazolino, dihydropyrano, dihydrothiopyrano, piperidino, piperazino, morpholino, thiomorpholino, tetrahydropyridino and tetrahydropyrimidino. Preferred groups are dihydropyrano, dihydrothiopyrano and piperidino. Further, said alicyclic group may have an alkyl group as a substituent, and 1 to 2 methyl or ethyl groups are preferred.

The term "alkyl" generally means a straight or branched alkyl having 1 to 10 carbon atoms, and lower alkyl having 1 to 6 carbon atoms are preferred. It illustratively includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 2-methylbutyl, n-hexyl and isohexyl.

The alkoxycarbonyl illustratively includes a methoxycarbonyl group, ethoxycarbonyl group, tertbutoxycarbonyl and benzyloxycarbonyl group, and ethoxycarbonyl group is particularly preferred.

The acyl group means aromatic acyl and aliphatic acyl groups. The aromatic acyl group includes benzoyl, 4-nitrobenzoyl, 4-tert-butylbenzoyl, benzenesulfonyl and toluenesulfonyl, and the aliphatic acyl group includes formyl, acetyl, propionyl, butyryl and valeryl groups. Above all, acetyl is preferred as the aliphatic acyl group.

Three tautomers can exist with respect to the compounds of the present invention, and the following formula (I) is only shown as its representative example. Thus, the compounds of the present invention include other tautomers, namely compounds (I') having a double bond in (1-2, 3a-3b and 4-5 positions) and compounds (I'') having a double bond in (1-3b, 2-3 and 3a-4 positions).



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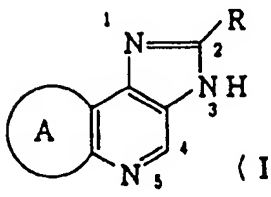
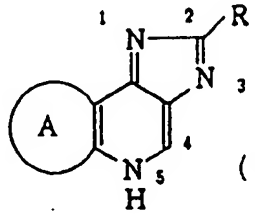


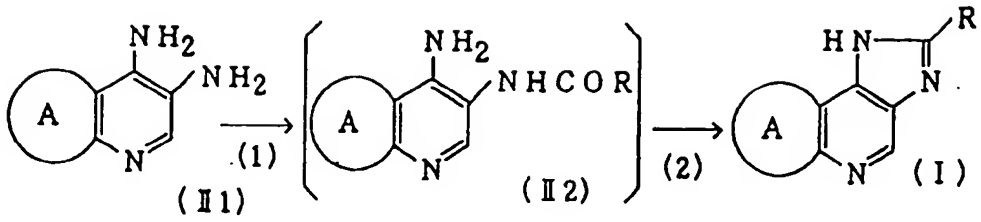
(I ')



(I '')

The compounds of the present invention include all the pharmaceutically acceptable salts of the compounds (I). In general, they can form a salt with inorganic acids, organic acids or acidic amino acids. The inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and orthophosphoric acid. The organic acids include formic acid, acetic acid, trifluoroacetic acid, oxalic acid, tartaric acid, fumaric acid, maleic acid, methanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid. The acidic amino acids include ornithine, aspartic acid and glutamic acid. In particular, preferable are salts with an inorganic acid (e.g. hydrochloric acid, phosphoric acid and orthophosphoric acid).

A typical process for the preparation of the compounds of the present invention is shown below.



In the above formulae, R and A each have the same significance as defined above.

First Step (Acylation)

This reaction is generally effected by reacting a compound (II1) with an acylating agent corresponding to the desired acyl group in an appropriate solvent. The reaction is carried out at a temperature from -10 to 50°C, preferably 0°C to around room temperature for 10 minutes to 5 hours, preferably for 30 minutes or 1 hour.

The solvent to be used includes triethylamine, pyridine, benzene, toluene, ether, methylene chloride, tetrahydrofuran, acetonitrile, dimethylformamide, chloroform, hexamethyltriamide, hexamethylphosphoric triamide, or a mixture thereof.

The acylating agent includes an acyl halide (e.g. benzoyl chloride), isoxazolyl chloride or a mixture of carboxylic acid and thionyl chloride. A condensing agent such as DCC or polyphosphoric acid may be used together.

Second Step (Cyclization)

The resultant compound (II2) can be used for the present step with or without isolation. The compound (I) can be obtained by heating the compound (II2) in an appropriate solvent at a temperature from about 50 to 400°C, preferably 100 to 250°C for 30 minutes to 10 hours, preferably for 1 to 5 hours.

This reaction is accelerated by neutralizing with a base, and the reaction is effected at comparatively low temperature, namely 50 to 200°C, preferably 100 to 150°C on an oil bath in the presence of a ring-closing agent.

As the solvent used herein there are exemplified an alcohol solvent such as diethylene glycol or triethylene glycol and an ethereal solvent such as 2-methoxyethyl ether.

The base includes sodium hydrogencarbonate, potassium hydroxide, sodium carbonate, sodium acetate, triethylamine and pyridine.

The ring-closing agent includes polyphosphoric acid, polyphosphoric acid ester, sulfuric acid, acetic acid, or phosphorus pentoxide.

Where the resultant compound (I) has NR^1 on the ring A (wherein $R^{1'}$ means an alkoxycarbonyl group), it can be subjected to the following step, if necessary.

(a) R^1: Hydrogen

The product can be obtained by subjecting the resultant alkoxycarbonyl compound to hydrolysis preferably in the presence of a catalyst in an appropriate solvent in a conventional manner.

The reaction is carried out at temperature from room temperature to 200°C, preferably 50 to 80°C, for 1 to 20 hours, preferably 4 to 6 hours.

The catalyst includes hydrobromic acid, hydrochloric acid, sulfuric acid, sodium hydroxide and potassium hydroxide.

The appropriate solvent includes acetic acid, methanol, ethanol, acetonitrile, or a mixture thereof. These solvents are used preferably in hydrous conditions.

(b) R^1: Acyl group

The compound obtained in Step (a) is subjected to acylation with an acylating agent such as acetic anhydride or acetyl chloride in a conventional manner, preferably in the presence of a base.

The reaction is carried out at a temperature from 0 to 100°C, preferably 10 to 30°C, for 30 minutes to 5 hours, preferably 1 to 3 hours.

The base includes pyridine, triethylamine, or 4-dimethylaminopyridine.

(c) R^1: Alkyl group

The product can be obtained by subjecting the alkoxycarbonyl compound to reduction, preferably in the presence of a reducing agent in an appropriate organic solvent.

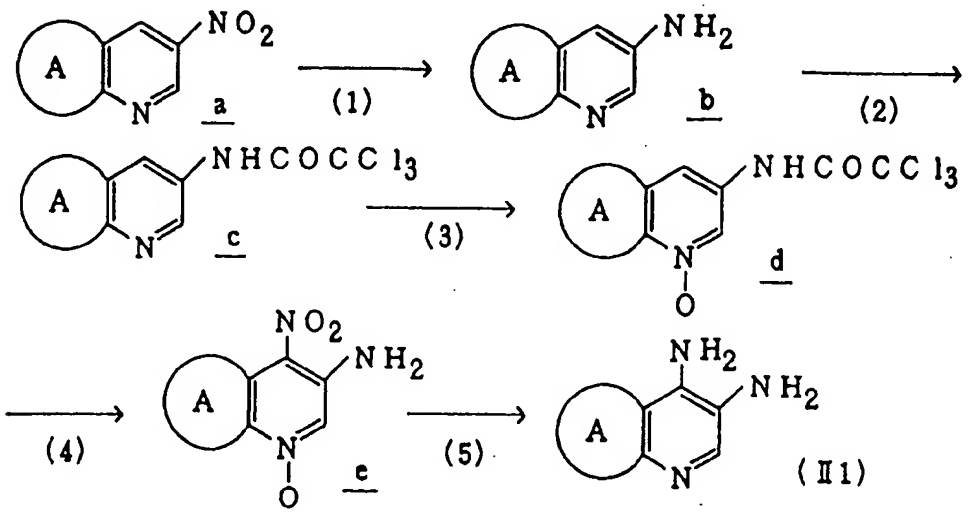
The appropriate solvent includes tetrahydrofuran, diethyl ether or dimethoxyethane.

Any reducing agent ordinarily usable for the reduction can be used herein, and preferable examples of the reducing agent are lithium aluminium hydride, sodium bis(2-methoxyethoxy)aluminium hydride, diisobutylaluminum hydride, sodium borohydride and lithium borohydride.

The compound (II1) usable as a starting material in said preparation can be synthesized in the following Process A and Process B. Further, the compound (II2) can be prepared directly according to Process C.

Process A

Synthetic Process of (II1)



In the above formulae, A has the same significance as previously defined.

(1) Compound b can be prepared by subjecting Compound a to hydrogenation.

This hydrogenation is carried out by using a hydrogenating catalyst in an appropriate inert solvent at a temperature from 10 to 50°C, preferably around room temperature for 30 minutes to 10 hours, preferably 5 to 7 hours.

The inert solvent usable herein includes water, acetic acid, methanol, ethanol and dioxane.

The hydrogenating catalyst includes platinum, palladium-carbon, radium-carbon or Raney nickel.

(2) Compound c can be prepared by reacting Compound b with trichloroacetyl chloride in an appropriate solvent, preferably in the presence of a base.

The appropriate solvent illustratively includes a halogenohydrocarbon (e.g. methylene chloride or chloroform) and an ether (e.g. tetrahydrofuran, dioxane, diethyl ether, diethyl ether or isopropyl ether.

The base includes triethylamine, sodium hydrogencarbonate, potassium hydroxide, sodium carbonate, sodium acetate or pyridine.

The reaction is effected at a temperature from 0 to 80°C, preferably around room temperature, for 10 minutes to 5 hours, preferably 20 minutes to 2 hours.

(3) Compound d can be prepared by oxidizing Compound c. Thus, the reaction is effected by reacting Compound c with m-chloroperbenzoic acid under mild conditions in a nonpolar solvent or by reacting Compound c with hydrogen peroxide in an acidic solvent such as acetic acid.

The nonpolar solvent includes methylene chloride, benzene, chloroform, hexane, or carbon tetrachloride. (4) Compound e can be prepared by nitrating Compound d and deprotecting the resulting compound.

The nitration is carried out by the use of fuming nitric acid or nitric acid, preferably in the presence of an acidic solvent, preferably, for example, sulfuric acid, at temperature from 10 to 200°C, preferably 30 to about 80°C over a period of 1 to 10 hours, preferably 3 to 6 hours. Higher temperatures may be required when nitric acid is used.

Deprotection is carried out in a conventional manner, for example, by treating with alkaline medium

such as aqueous ammonia or sodium hydroxide.

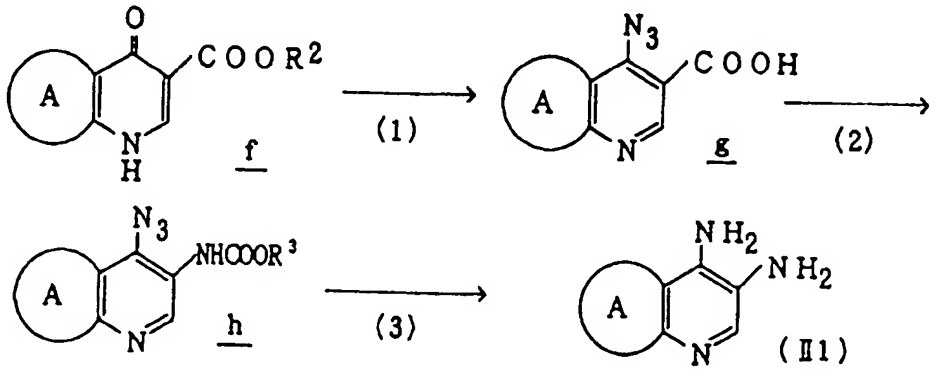
(5) Compound (II1) can be prepared by hydrogenating Compound e by the use of a hydrogenating catalyst in an appropriate inert solvent at temperature from 10 to 50°C, preferably around room temperature over a period of 30 minutes to 10 hours, preferably 5 to 7 hours.

The inert solvent includes water, acetic acid, methanol, ethanol or dioxane.

The hydrogenating catalyst includes Raney nickel, Platinum-carbon, palladium-carbon or radium-carbon, and, in particular, Raney nickel is preferred.

Process B

Synthetic Process of (II1)



In the above formulae, R^2 and R^3 each mean a lower alkyl group, and A has the same significance as previously defined.

(1) Compound f is allowed to react with phosphorus trichloride, phosphorous pentachloride, or phosphorus oxychloride (e.g. metaphosphoryl chloride) to give the 3-chloro compound. Then, the 3-azido compound g is obtained by treating the 3-chloro compound with a metal azide such as sodium azide, lead azide or ferrous azide.

(2) Compound g is allowed to react with ethyl chloroformate, preferably in the presence of a base, in an appropriate solvent to give an acid anhydride. Then, the acid anhydride is allowed to react with a metal azide to give an azide carbonyl, CON_3, which is refluxed with an appropriate alcohol to give Compound h.

The solvent for the reaction may include tetrahydrofuran, dioxane, diethyl ether, toluene or acetonitrile.

The base to be used may be triethylamine, sodium bicarbonate, potassium hydroxide, sodium carbonate or pyridine.

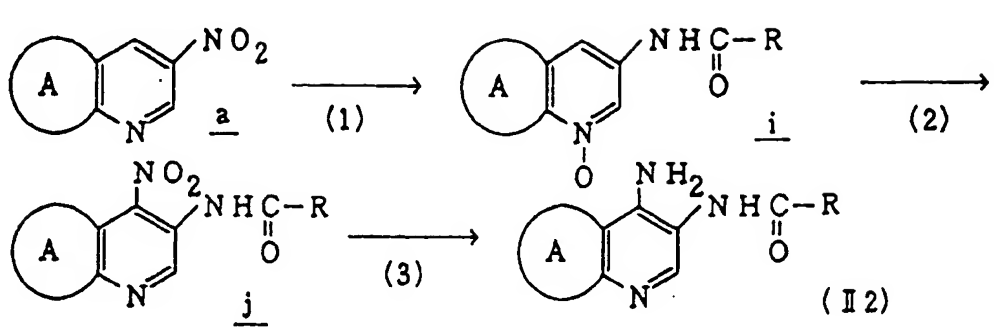
The alcohol includes alcohols having a branched alkyl chain such as isopropanol or tert-butanol.

(3) Compound h is subjected to reduction in a conventional manner and then deacylated at the 3 position to give Compound (II1).

All the reducing agents ordinarily used for reduction can be used herein, and stannous chloride hydrate is most preferred for this reaction.

Process C

Synthetic Process of (II2)



In the above formulae, A and R have the same significance as previously defined.

(1) Compound i is obtained by subjecting Compound a to oxidation, and then reduction, and reacting the resulting amino/oxide with an acylating agent.

Oxidation can be carried out in the same manner as in Process A (3) for the production of Compound (II1).

Reduction can be carried out in the same manner as in Process A (1) for the production of Compound (II1).

The acylating agent includes various agents containing the desired acyl group and illustratively includes a chloride (e.g. isoxazolyl chloride), aroyl chloride (e.g. benzoyl chloride), acid chloride, acid anhydride, or a combination of carboxylic acid and thionyl chloride.

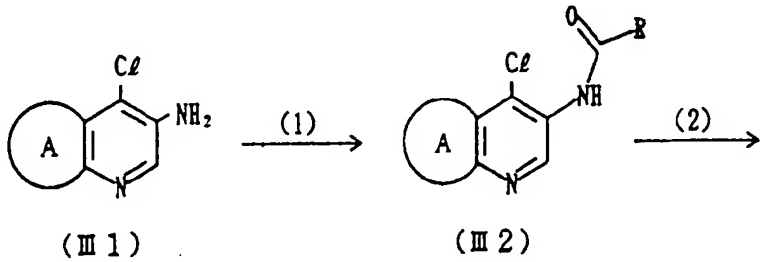
(2) Compound i is nitrated with fuming nitric acid, and the resulting nitrated oxide is subjected to ordinary deoxygenation in the presence of a tertiary phosphine type deoxygenating reducing agent such as phosphorus tribromide, phosphorus trichloride or triphenylphosphine to give Compound j.

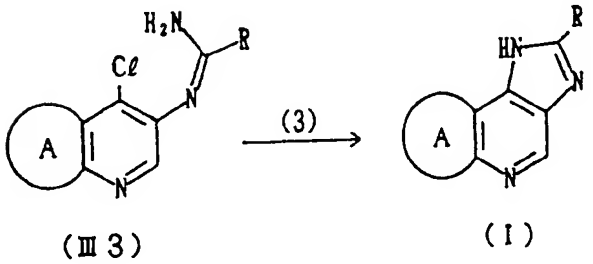
(3) Compound (II2) is obtained by reducing Compound j.

Reduction is carried out in the same manner as in Process A (1) for the production of Compound (II1).

Further, the compounds of the present invention can be prepared by adopting the alternative process as shown in the following Reaction Scheme 2.

Reaction Scheme 2





In the above formulae, R and A each have the same significance as previously defined.

First Step

This step includes a process for preparing Compound (III2) which comprises acylating Compound (III1) with an acyl halide of R-COC1. This reaction is generally carried out at a temperature from -20 to 60°C, preferably at from -10 to 10°C for a period of several minutes to several hours. As a solvent, there can be used, for example, methylene chloride, dimethylformamide, chloroform or tetrahydrofuran.

Second Step

This step includes a process for preparing Compound (III3) which comprises reacting Compound (III2) with a chlorinating agent and subsequently with ammonia. In general, the reaction is carried out using a chlorinating agent such as phosphorus pentachloride and phosphorus oxychloride, and a base such as pyridine and triethylamine at a temperature from 0 to 60°C, preferably from 30 to 50°C over a period of several minutes to several hours, and then treating the resulting product with ammonia. As a solvent, there can be employed, for example, methylene chloride or chloroform, tetrahydrofuran.

Third Step

Compound (I) is obtained by subjecting Compound (III3) to cyclization under heating. As a solvent there can be used an inert solvent having a high boiling point, such as N-methyl-2-pyrrolidone, a mixture of biphenylether or biphenyl. The reaction is ordinarily carried out at a temperature from 50 to 250°C over a period of several minutes to several hours.

The starting materials used in the above-mentioned alternative process as shown in Reaction Scheme 2 can be prepared by methods hereinafter described in Reference Example 5.

The compounds of the present invention can be orally or parenterally administered. For oral administration, the compounds of the present invention can be formulated in conventional formulations, for example, solid forms such as tablets, powders, granules or capsules; liquid forms such as solutions; oil suspensions; or syrups or elixirs. For parenteral administration, the compounds of the present invention can be formulated in aqueous or oily suspended injections. The formulations may contain ordinary disintegrators, binders, lubricants, aqueous solvents, oily solvents, emulsifiers or suspenders. Other adjuvants such as preservatives or stabilizers may be included therein.

Appropriate dosages of the compounds of the present invention vary depending upon administration routes, ages, body weights, conditions of the particular patient and types of diseases. In general, an appropriate daily dosage for the oral route is 0.05 to 500 mg, preferably 0.1 to 200 mg, and an appropriate daily dosage for the parenteral route is 0.01 to 300 mg, preferably 0.05 to 100 mg. The dosage may be administered after division into two to five portions.

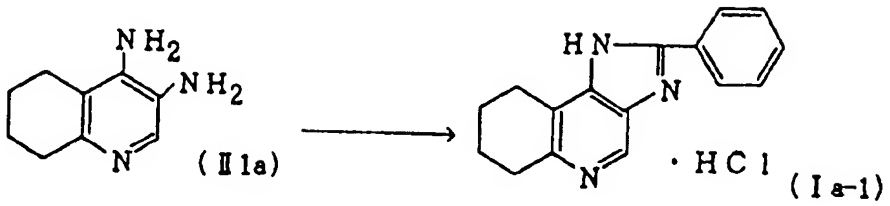
The following working examples will explain the present invention in more detail, but the scope of the present invention should not be limited thereto. The production of the compounds of the present invention based on Reaction Scheme 1 is illustrated by Examples 1 to 36, and the production of the compounds based on Reaction Scheme 2 is illustrated by Examples 37 to 44, respectively.

The abbreviations used in the Examples have the following meanings.

Me : Methyl
Et : Ethyl
iPr : Isopropyl
t-Bu : tert-Butyl
DMSO : Dimethyl sulphurised

Example 1

2-Phenyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]-quinoline (Ia-1)



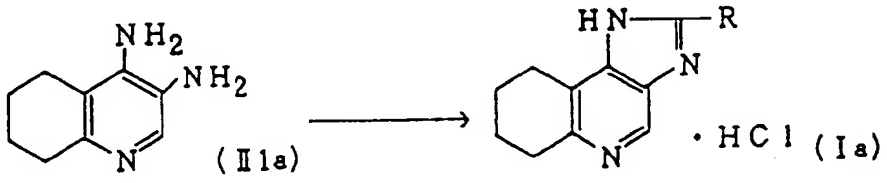
To a solution of 400 mg of 3,4-diamino-5,6,7,8-tetrahydroquinoline (II1a) (synthesized in Reference Example 1 below) in 5 ml of pyridine is added 380 mg of benzoyl chloride with ice cooling, and the resultant mixture is stirred at room temperature for 30 minutes. The mixture is admixed with 261 mg of sodium acetate and 8 ml of ethylene glycol, and the mixture is heated at 150°C (oil bath temperature) for 3.5 hours. After the mixture is concentrated in vacuo to remove the solvent, the residue is chromatographed on a silica gel column, and the purified product is mixed with conc. hydrochloric acid to give the hydrochloride as crude crystals. The crude product is recrystallized from methanol-isopropanol to give 595 mg of the titled product (Ia-1) as colorless crystals melting at 292 to 299°C.

Yield: 85%

Elemental Analysis (%) $C_{16}H_{16}N_3Cl$

Calculated: C, 67.24; H, 5.64; N, 14.70; Cl, 12.41 Found: C, 67.11; H, 5,83; N, 14.63; Cl, 12.33 NMR (d_6-DMSO) δ : 1.82 (4H, br.s); 2.64 (2H, br.s); 2.73 (2H, br.s); 7.23 to 7.40 (5H, m); 8.30 (1H, s)

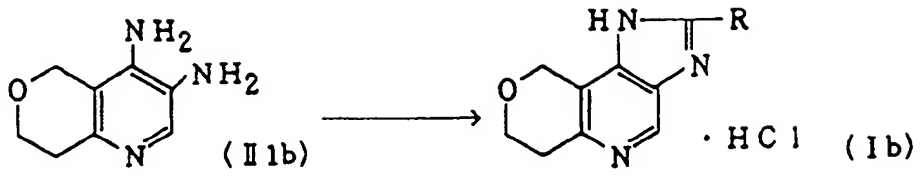
Examples 2 to 6



The following compounds are obtained by the use of Compound (II1a) as a starting compound in the same manner as in Example 1.

Ia-2 (R = 4-chlorophenyl): (Example 2)
mp.: 312 to 319°C (dec.)
NMR (D_2O) δ: 1.91 (4H, m); 2.68 (2H, m); 2.95 (2H, m); 6.83 (2H, m); 7.19 (2H, m); 8.37 (1H, s)
Ia-3 (R = 2-thienyl): (Example 3)
mp.: 334 to 337°C (dec.)
NMR (D_2O) δ: 1.86 (4H, m); 2.70 (2H, m); 2.78 (2H, m); 7.03 (1H, m); 7.34 (1H, m); 7.64 (1H, m); 8.30 (1H, s)
Ia-4 (R = 3-thienyl): (Example 4)
mp.: 331 to 334°C (dec.)
NMR (D_2O) δ: 1.88 (4H, m); 2.76 (4H, m); 7.13 (1H, m); 7.47 (1H, m); 7.79 (1H, m); 8.35 (1H, s)
Ia-5 (R = 2-furyl): (Example 5)
mp.: 288 to 292°C (dec.)
NMR (D_2O) δ: 1.92 (4H, m); 2.78 (2H, m); 2.85 (2H, m); 6.69 (1H, m); 7.03 (1H, m); 7.75 (1H, m); 8.51 (1H, s)
Ia-6 (R = 3-methyl-5-isoxazolyl): (Example 6)
mp.: 272 to 280°C (dec.)
NMR (DMSO) δ: 1.91 (4H, br.s); 2.41 (3H, s); 3.11 (4H, br.s); 3.42 (1H, br.s, NH); 7.57 (1H, s); 9.29 (1H, s)

Examples 7 to 12

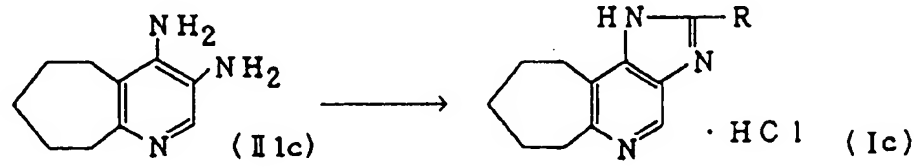


(II 1b) (Ib)

The following compounds are obtained by the use of Compound (II1b) as a starting compound in the same manner as in Example 1.

Ib-1 (R = 4-chlorophenyl): (Example 7)
mp.: 291 to 297°C (dec.)
NMR (D_2O) δ: 3.17 (2H, m); 4.20 (2H, m); 4.86 (2H, s); 6.99 (2H, d); 7.34 (2H, d); 8.63 (1H, s)
Ib-2 (R = 2-thienyl): (Example 8)
mp.: 285 to 288°C (dec.)
NMR (DMSO) δ: 3.16 (2H, t); 3.40 (1H, br.s); 4.08 (2H, t); 5.12 (2H, s); 7.34 (1H, m); 7.97 (1H, m); 8.39 (1H, m); 9.16 (1H, s)
Ib-3 (R: 3-thienyl): (Example 9)
mp.: 300 to 306°C (dec.)
NMR (D_2O) δ: 3.06 (2H, t); 4.16 (2H, t); 4.92 (2H, s); 7.28 (1H, m); 7.51 (1H, m); 7.95 (1H, m); 8.63 (1H, s)
Ib-4 (R = 2-furyl): (Example 10)
mp.: 270 to 274°C (dec.)
NMR (D_2O) δ: 3.13 (2H, m); 4.19 (2H, t); 4.98 (2H, s); 6.72 (1H, m); 7.20 (1H, m); 7.97 (1H, s); 8.77 (1H, s)
Ib-5 (R = 3-methyl-5-isoxazolyl): (Example 11)
mp.: 266 to 272°C (dec.)
NMR (D_2O) δ: 2.42 (3H, s); 3.24 (2H, t); 4.24 (2H, t); 5.10 (2H, s); 7.11 (1H, s); 9.05 (1H, s)
Ib-6 (R = 2-pyridyl) (dihydrochloride): (Example 12)
mp.: 265 to 281°C (dec.)
NMR (D_2O) δ: 3.13 (2H, t); 4.19 (2H, t); 5.00 (2H, s); 7.58 (1H, m); 7.95 to 7.97 (2H, m); 8.63 (1H, d); 8.68 (1H, s)

Examples 13 to 19



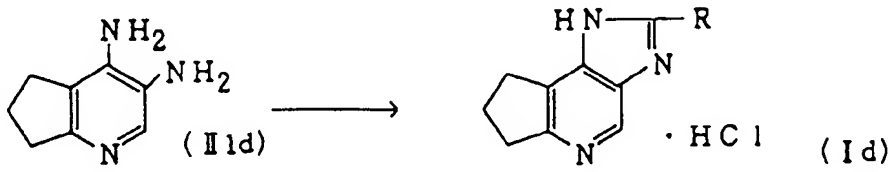
(II 1c) (Ic)

The following compounds are obtained by the use of Compound (II1c) as a starting compound in the same manner as in Example 1.

Ic-1 (R = phenyl): (Example 13)
mp.: 253 to 258°C (dec.)
NMR (DMSO) δ: 1.72 to 1.96 (6H, m); 3.01 (4H, m); 7.31 to 7.59 (5H, m); 8.30 (1H, s)
Ic-2 (R = 4-chlorophenyl): (Example 14)
mp.: 298 to 320°C (dec.)
NMR (DMSO) δ: 1.68 to 1.92 (6H, m); 3.33 (4H, m); 7.72 (2H, d); 8.44 (2H, d); 9.06 (1H, s)
Ic-3 (R = 2-thienyl): (Example 15)
mp.: 271 to 274 °C
NMR (D_2O) δ: 1.72 to 1.96 (6H, m); 3.03 (4H, m); 7.07 (1H, t); 7.52 (1H, d); 7.66 (1H, d); 8.23 (1H, s)
Ic-4 (R = 3-thienyl): (Example 16)
mp.: 264 to 271°C
NMR (D_2O) δ: 1.74 to 1.99 (6H, m); 3.07 (4H, m); 7.37 (1H, m); 7.52 (1H, m); 8.03 (1H, m); 8.40 (1H, s)

Ic-5 (R = 2-furyl): (Example 17)
mp.: 250 to 261°C (dec.)
NMR (D_2O) δ: 1.75 to 1.99 (6H, m); 3.10 (4H, m); 6.74 (1H, m), 7.24 (1H, m); 7.82 (1H, d); 8.52 (1H, s)
Ic-6 (R = 3-isoxazolyl): (Example 18)
mp.: 191 to 193°C (dec.)
NMR (D_2O) δ: 1.78 to 2.02 (6H, m); 3.24 (4H, m); 7.15 (1H, m); 8.86 (1H, s); 8.96 (1H, m)
Ic-7 (R = 3-methyl-5-isoxazolyl): (Example 19)
mp.: 243 to 260°C (dec.)
NMR (D_2O) δ: 1.77 to 2.03 (6H, m); 2.43 (3H, s); 3.23 (4H, m); 7.14 (1H, s); 8.84 (1H, s)

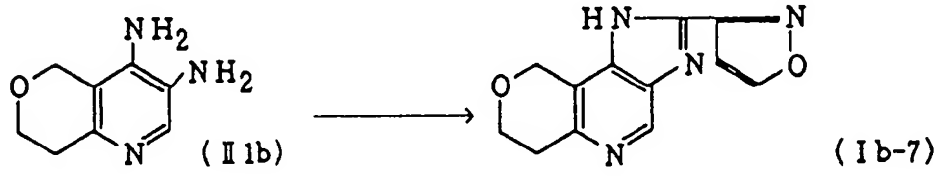
Examples 20 to 24



The following compounds are obtained by the use of Compound (II1d) as a starting compound in the same manner as in Example 1.
Id-1 (R = 3-isoxazolyl): (Example 20)
mp.: 252 to 256°C (dec.)
NMR (D_2O) δ: 2.46 (2H, m); 3.27 (2H, t); 3.31 (2H, t); 7.09 (1H, m) 8.94 (1H, m); 8.95 (1H, s)
Id-2 (R = 3-methyl-5-isoxazolyl): (Example 21)
mp.: 290 to 293°C (dec.)
NMR (D_2O) δ: 2.42 (3H, s); 2.45 (2H, m); 3.25 (2H, m); 3.30 (2H, m); 7.05 (1H, s); 8.91 (1H, m)
Id-3 (R = 2-pyridyl): (Example 22)
mp.: 242 to 256°C (dec.)
NMR (D_2O) δ: 2.38 (2H, m); 3.17 (4H, t); 7.67 (1H, m); 8.00 to 8.12 (2H, m); 8.67 (1H, m); 8.76 (1H, s)
Id-4 (R = 4-methoxyphenyl): (Example 23)
mp.: 309 to 316°C (dec.)
NMR (D_2O) δ: 2.45 (2H, m); 2.86 to 2.99 (4H, m); 3.69 (3H, s); 6.54 (2H, d); 7.19 (2H, d); 8.30 (1H, s)
Id-5 (R = 4-methylphenyl): (Example 24)
mp.: 330°C (dec.)
NMR (D_2O) δ: 2.18 (3H, s); 2.22 (2H, m); 2.88 (4H, m); 6.92 (2H, d); 7.19 (2H, d); 8.25 (1H, s)

Example 25

2-(3-Isoxazolyl]-1,6,7,9-tetrahydroimidazo[4,5-d]pyrano[4,3-b]pyridine (Ib-7)

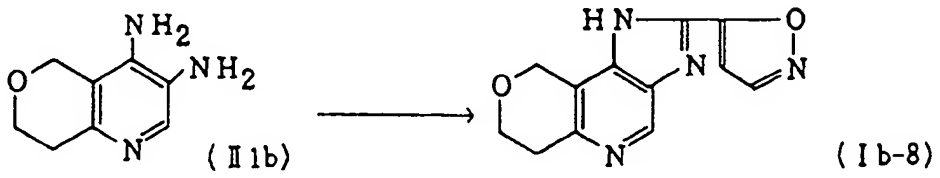


To a solution of 5.88 g of 3,4-diamino-7,8-dihydro-5H-pyrano[4,3-b]pyridine (II1b) (synthesized in Reference Example 1) in 50 ml of dimethylformamide is added a solution of 4.43 g of 3-isoxazolyl chloride in 4.7 ml of methylene chloride with ice cooling, and the resultant mixture is stirred at room temperature for 45 minutes, mixed with 4.7 ml of triethylamine and stirred for 1 hour. The reaction mixture is filtered, and the resultant crystals are mixed with 500 mg of sodium acetate and 79 ml of ethylene glycol and heated at 150°C (on an oil bath) for 5 hours. The solvent is evaporated in vacuo to dryness, and the resulting residue is chromatographed on a silica gel column, eluting with 10% methanol/chloroform. The product is recrystallized from chloroform-isopropanol to give 5.76 g of Compound (Ib-7) as white crystals melting at 345 to 347°C (dec.). Yield: 74%
Elemental Analysis (%) $C_{12}H_{12}N_4O_2$

Calculated: C, 59.50; H, 4.16; N, 23.12
Found: C, 59.33; H, 4.23; N, 22.91
NMR (d_6-DMSO) δ : 2.98 (2H, t); 4.05 (2H, t); 5.01 (2H, s); 7.23 (1H, d); 8.83 (1H, s); 9.21 (1H, d)

Example 26

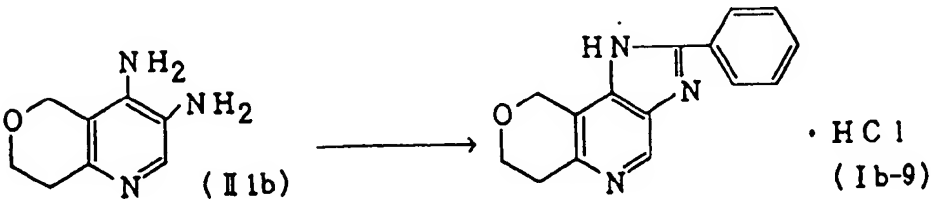
2-(5-Isoxazolyl)-1,6,7,9-tetrahydroimidazo[4,5-d]pyrano[4,3-b]-pyridine (Ib-8)



To a solution of 264 mg of 5-isoxazolecarboxylic acid in a mixture of 3.5 ml of hexamethylphosphoric triamide and 0.4 ml of acetonitrile is dropwise added 272 mg of thionyl chloride at 0°C. The resultant mixture is stirred at the same temperature for 30 minutes, mixed with 350 mg of Compound (II1b) and stirred for 4 hours. The reaction mixture is diluted with ice water and neutralized with sodium bicarbonate. The precipitated crystals are dissolved in 14 ml of ethylene glycol, heated at 150°C for 3.5 hours and the solvent is evaporated in vacuo. The residue is chromatographed on a silica gel column, eluting with methylene chloride-methanol (30 : 1). The product is recrystallized from methanol-ethyl acetate to give 170 mg of Compound (Ib-8) as colorless crystals melting at 329 to 333°C (dec.). Yield: 33%
Elemental Analysis (%) $C_{12}H_{10}N_4O_2 \cdot 1/3H_2O$
Calculated: C, 58.06; H, 4.33; N, 22.57
Found: C, 58.06; H, 4.35; N, 22.42
NMR (D_6-DMSO) δ : 2.99 (2H, t); 4.05 (2H, t); 5.01 (2H, s); 7.22 (1H, d); 8.82 (1H, d); 8.84 (1H, s)

Example 27

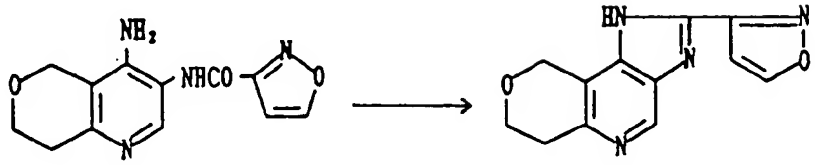
2-Phenyl-1,6,7,9-tetrahydroimidazo[4,5-d]pyrano[4,3-b]pyridine (Ib-9)



To 6 g of polyphosphoric acid are added 400 mg of Compound (II1b) and 347 mg of benzoic acid, and the mixture is heated on an oil bath at 130°C for 5 hours. After cooling, the reaction mixture is mixed with ice water, made alkaline with aqueous ammonia and the precipitated crystals are filtered. The filtrate is extracted with 10% methanol/chloroform. The crystals are combined with the extract and chromatographed on a silica gel column, eluting with 5% methanol/chloroform. The product is converted into the hydrochloride in a conventional manner and recrystallized from methanol/isopropanol to give 559 mg of the titled Compound (Ib-9) as white crystals. Yield: 89%
mp.: 269 to 286°C (dec.)
NMR (DMSO) δ: 3.17 (2H, t); 3.42 (1H, br.s); 4.90 (2H, t); 5.16 (2H, s); 7.62 to 7.66 (3H, m); 8.35 to 8.44 (2H, m); 9.24 (1H, s)
Elemental Analysis (%) $C_{15}H_{13}ON_3 \cdot HCl$
Calculated: C, 62.61; H, 4.90; N, 14.60; Cl, 12.32
Found: C, 62.67; H, 5.01; N, 14.80; Cl, 12.38

Example 28

Alternative Synthetic Method of Compound (Ib-7)



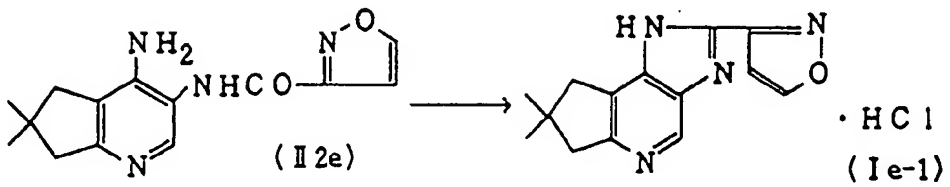
(II 2 b) (I b - 7)

A mixture of 260 mg of isoxazolylaminopyridine (II2b) (synthesized in Reference Example 2) and 4 ml of ethylene glycol is heated at 150°C for 3 hours. The solvent is evaporated in vacuo, and the residue is dissolved while heated in aqueous ethanol and decolored over active carbon. The precipitated solid is filtered to give 206 mg of Compound (Ib-7) as colorless crystals. Yield: 85%. The crystals were identified as the compound obtained in Example 25 by comparing the melting point and spectra. Further, the following salts of Compound (Ib-7) are synthesized in a conventional manner.

(1) Hydrochloride: mp. 321 to 325°C (dec.)
Elemental Analysis (%) $C_{12}H_{11}N_4O_2Cl \cdot 1/4H_2O$
Calculated: C, 50.89; H, 4.09; N, 19.78; Cl, 12.52
Found: C, 50.90; H, 4.13; N, 19.50; Cl, 12.38
(2) Phosphate: mp. 239 to 241°C (dec.)
Elemental Analysis (%) $C_{12}H_{13}N_4O_6P \cdot H_2O$
Calculated: C, 40.23; H, 4.22; N, 15.63
Found: C, 40,05; H, 4.19; N, 15.39
(3) Methanesulfonate: mp. 219 to 222°C (dec.)
Elemental Analysis (%) $C_{13}H_{14}N_4O_5S \cdot 1/3H_2O$
Calculated: C, 45.35; H, 4.29; N, 16.21; S, 9.31
Found: C, 45.17; H, 4.16; N, 16.19; S, 9.56
(4) Maleate: mp. 331 to 336°C (dec.)
Elemental Analysis (%) $C_{16}H_{14}N_4O_6$
Calculated: C, 53.63; H, 3.93; N, 15.63
Found: C, 53.73; H, 3.93; N, 15.62

Example 29

2-(3-Isoxazolyl)-7,7-dimethyl-1H-imidazo(4,5-d]-cyclopenta[b]pyridine (Ie-1)

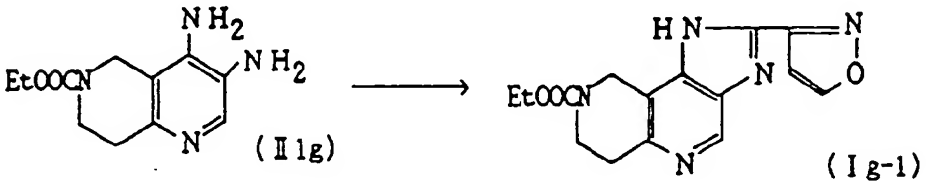


(II 2e) · HCl (I e-1)

A mixture of 2.05 g of 4-amino-3-(3-isoxazolylamino)-6,6-dimethylcyclopenta[b]pyridine (II2e) and 21 ml of ethylene glycol is heated at 150°C for 3.5 hours, and the solvent is evaporated in vacuo. The residue is chromatographed on a silica gel column, eluting with methylene chloride-methanol (30/1). The product is dissolved in methanol and mixed with methanolic hydrochloric acid to give 1.90 g of Compound (Ie-1).
Yield: 82%
mp.: 270 to 272°C
Elemental Analysts (%) $C_{14}H_{15}N_4OCl$
Calculated: C, 57.83; H, 5.19; N, 19.26; Cl, 12.19
Found: C, 57.53; H, 5.31; N, 19.09; Cl, 12.31
NMR (d_6-DMSO) δ : 1.26 (6H, s); 3.08 (2H, s); 3.12 (2H, s); 7.40 (1H, d); 9.34 (1H, d)

Example 30

2-(3-Isoxazolyl)-8-ethoxycarbonyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]naphthylidine (Ig-1)



(II1g) (Ig-1)

To a solution of 274 mg of 3-isoxazolecarboxylic acid in a mixture of 3.5 ml of hexamethyl phosphotriamide and 0.5 ml of acetonitrile is dropwise added 288 mg of thionyl chloride at 0°C, and the resultant mixture is stirred at the same temperature for 30 minutes. To the mixture is added 520 mg of 3,4-diamino-6-ethoxycarbonyl-5,6,7,8-tetrahydro[1,6]naphthylidine (II1g) (synthesized in Reference Example 3), and the mixture is stirred for 4 hours. The reaction mixture is diluted with ice water, neutralized with sodium bicarbonate and extracted with methylene chloride, the extract is dissolved in 15 ml of ethylene glycol and heated at 150°C for 4 hours. The solvent is evaporated in vacuo, and the residue is chromatographed on a column of silica gel, eluting with methylene chloride-methanol (50 : 1). The product is recrystallized from methanol/ethyl acetate to give 410 mg of Compound (Ig-1). Yield: 60%

mp.: 271 to 273°C (dec.)

Elemental Analysis (%) $C_{15}H_{15}N_5O_3$

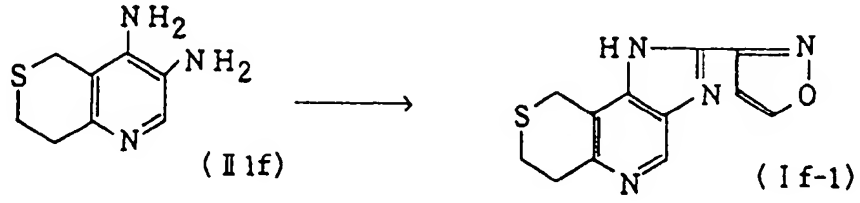
Calculated: C, 57.50; H, 4.82; N, 22.35

Found: C, 57.47; H, 5.02; N, 22.25

NMR (d_6-DMSO) δ : 1.24 (3H, t); 2.99 (2H, t); 3.79 (2H, t); 4.13 (2H, q); 4.90 (2H, s); 7.28 (1H, d); 8.82 (1H, s); 9.22 (1H, d)

Example 31

2-(3-Isoxazolyl)-1,6,7,9-tetrahydroimidazo[4,5]-thiopyrano[4,3-b]pyridine (If-1)



(II1f) (If-1)

Compound (II1f) is used as a starting compound in the same manner as in Example 26 to give Compound (If-1).

mp.: 253 to 255°C (dec.)

Elemental Analysis (%) $C_{12}H_{10}N_4OS \cdot 1/6H_2O$

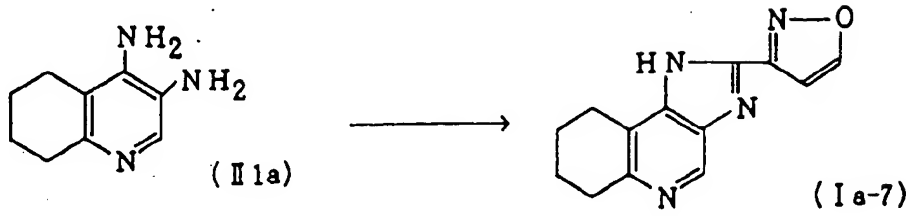
Calculated figure: C, 55.16; H, 3.99; N, 21.44; S, 12.27

Measured figure : C, 55.17; H, 4.21; N, 21.23; S, 12.05

NMR (D_6-DMSO) δ: 3.04 (2H, t); 3.20 (2H, t); 4.13 (2H, s); 7.24 (1H, d); 8.81 (1H, s); 9.21 (1H, d); 13.76 (1H,br.s, NH)

Example 32

2(3-Isoxazolyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline (Ia-7)



(II1a) (Ia-7)

Compound (II1a) is used as a starting compound in the same manner as in Example 26 to give Compound (Ia-7).

mp.: 222 to 225°C

Elemental Analysis (%) $C_{13}H_{12}N_4O$

Calculated: C, 63.41; H, 5.18; N, 22.75

Found: C, 63.42; H, 5.18; N, 22.48

NMR (d_6-DMSO) δ: 1.86 (4H, m); 2.92 (2H, m); 2.99 (2H, m); 7.22 (1H, d); 8.75 (1H, s); 9.19 (1H, d)

Example 33

2-(3-Isoxazolyl)-1H-imidazo[4,5-d]cyclopenta[b] pyridine (Id-1)

Compound (II1d) is used as a starting compound in the same manner as in Example 26 to give Compound (Id-1).

mp.: 250 to 255°C

Elemental Analysis (%) $C_{12}H_{10}N_4O \cdot 1/3H_2O$

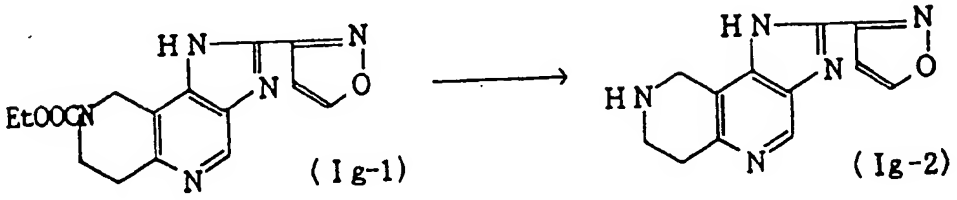
Calculated: C, 62.06; H, 4.63; N, 24.12

Found: C, 61.97; H, 4.61; N, 23.97

NMR (d_6-DMSO) δ: 2.18 (2H, m); 3.02 (2H, t); 3.14 (2H, t); 7.25 (1H, d); 8.77 (1H, s); 9.22 (1H, d)

Example 34

2-(3-Isoxazolyl)-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]-naphthylidine (Ig-2)



(Ig-1) (Ig-2)

A mixture of 490 mg of Compound (Ig-1) obtained in Example 30 and 25% hydrobromic acid/acetic acid (25 ml) was stirred at 70°C for 5 hours. After the solvent is evaporated in vacuo, the residue is neutralized with aqueous sodium bicarbonate and concentrated in vacuo to dryness. The residue is shaken with chloroform/methanol and the resultant solution is concentrated. The residue is chromatographed on an alumina column, eluting with methylene chloride-methanol (10 : 1). The product is recrystallized from methanol-ethyl acetate to give 335 mg of Compound (Ig-2) as crystals melting at 278 to 281°C (dec.). Yield: 89%

Elemental Analysis (%) $C_{12}H_{11}N_5O$

Calculated: C, 59.74; H, 4.59; N, 29.02

Found: C, 59.54; H, 4.71; N, 29.31

NMR (d_6-DMSO) δ: 2.87 (2H, t); 3.10 (2H, t); 4.15 (2H, s); 7.21 (1H, d); 8.76 (1H, s); 9.18 (1H, d)

Example 35

2-(3-Isoxazolyl)-8-acetyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]naphthylidine (Ig-3)

To a mixture of 95 mg of Compound (Ig-2) obtained in the foregoing Example and 5 ml of methylene chloride are added 160 mg of triethylamine and 160 mg of acetic anhydride and the resultant mixture is stirred at room temperature for 1 hour. After the solvent is evaporated in vacuo, the residue is recrystallized from ethyl acetate-methylene chloride to give 68 mg of the acetylate (Ig-3).
Yield: 61%
mp.: 236 to 240°C
Elemental Analysis (%) $C_{14}H_{13}N_5O_2 \cdot 1/4H_2O$
Calculated: C, 58.43; H, 4.73; N, 24.33
Found: C, 58.52; H, 4.62; N, 24.20
NMR (d_6-DMSO) δ : 2.52 (3H, s); 3.31 (2H, t); 3.96 (2H, t); 5.35 (2H, s); 7.13 (1H, d); 8.57 (1H, d); 8.99 (1H, s)

Example 36

2-(3-isoxazolyl)-8-methyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]naphthylidine (Ig-4)

To a solution of 680 mg of Compound (Ig-1) obtained in Example 30 is added 330 mg of lithium aluminum hydride, and the resultant mixture is refluxed for 6 hours. After the reaction mixture is chilled with ice, the mixture is mixed with 0.5 ml of 2N aqueous sodium hydroxide and stirred at room temperature for 30 minutes. The precipitate is filtered and the filtrate is concentrated. The residue is chromatographed on an alumina column, eluting with methylene chloride-methanol (50/1). The product is treated with hydrochloric acid to give 340 mg of Compound (Ig-4) hydrochloride. Yield: 53%
mp.: 243 to 247°C (dec.)
Elemental Analysis (%) $C_{13}H_{15}N_5OCl \cdot H_2O$
Calculated: C, 45.09; H, 4.94; N, 20.22; Cl, 24.48
Found: C, 45.07; H, 5.07; N, 19.95; Cl, 20.75

Reference Example 1

Preparation of 3,4-diamino-5,6,7,8-tetrahydroquinoline (II1a)

(1) 3-Amino-5,6,7,8-tetrahydroquinoline 1

A suspension of 15.8 g of 3-nitro-5,6,7,8-tetrahydroquinoline [synthesized according to the method as described in Bull. Chem. Soc. Jpn. Vol. 63 (1990), 2820] and 1.6 g of 5% palladium carbon in 300 ml of methanol is hydrogenerated at ordinary temperature under atmospheric pressure. The catalyst is filtered off, and the filtrate is concentrated in vacuo to remove the solvent. The resultant crude product is recrystallized from methylene chloride-isopropyl ether to give 12.76 g of the titled compound 1. Yield: 97%
mp.: 97 to 98°C

(2) 3-Trichloroacetylamino-5,6,7,8-tetrahydroquinoline 2

To 130 ml of methylene chloride are added 12.69 g of Compound 1 obtained in the above step (1) and 2.4 ml of triethylamine, and a solution of 10.5 ml of trichloroacetyl chloride in 30 ml of methylene chloride is dropwise added with ice cooling and under stirring over a period of 7 minutes. The reaction mixture is stirred at room temperature for 20 minutes, mixed with saturated saline, made weakly alkaline with aqueous ammonia and the organic layer is separated. The aqueous layer is shaken with methylene chloride. The organic layers are combined, washed with saturated saline, dried over anhydrous magnesium sulfate and concentrated to remove the solvent. The residue is chromatographed on a silica gel column, eluting with 10% methanol/methylene chloride. The product is recrystallized from ethyl acetate to give 24.21 g of the titled compound 2. Yield: 96%
mp.: 157 to 159°C

(3) 3-Trichloroacetylamino-5,6,7,8-tetrahydroquinoline-1-oxide 3

To a solution of 24.03 g of Compound 2 obtained in the above step (2) in 40 ml of methylene chloride is added 21.2 g of 80% m-chloroperbenzoic acid at room temperature, and the resultant mixture is stirred for 45 minutes. The reaction mixture is mixed with isopropyl ether and the crystals are filtered to give 25.06 g of the titled compound 3 as crystals. Yield: 99%
mp.: 244 to 246°C (dec.)

(4) 3-Amino-4-nitro-5,6,7,8-tetrahydroquinoline-1-oxide 4

A mixture of 1.00 g of Compound 3 obtained in the above step (3) and 5.0 ml of fuming nitric acid (d = 1.52) is stirred at 55°C on an oil bath for 5 hours. The fuming nitric acid is evaporated in vacuo, and the residue is neutralized with aqueous ammonia and heated at 60°C on an oil bath for 2 hours. The reaction mixture containing crystals is mixed with 10 ml of 50% isopropyl ether/isopropanol, and the resulting precipitate is filtered. The filtrate is concentrated in vacuo and extracted with 10% methanol/chloroform. The crystals are combined with the residue and chromatographed on an alumina column, eluting with 2% methanol/chloroform. The product is recrystallized from methylene chloride-isopropanol to give 525 mg of the titled compound 4 as brownish red crystals.
Yield: 78%
mp.: 199 to 201°C

(5) 3,4-Diamino-5,6,7,8-tetrahydroquinoline (II1a)

A mixture of 5.00 g of Compound 4 obtained in the above step (4) and 12.9 g of Raney nickel in methanol is hydrogenated at ordinary temperature under atmospheric pressure. The catalyst is filtered off, and the filtrate is concentrated in vacuo to remove the solvent. The residue is chromatographed on an alumina column, eluting with 5% methanol/chloroform. The product is recrystallized from methylene chloride-ethyl acetate to give 3.37 g of the titled compound (II1a) as crystals. Yield: 86%
mp.: 169 to 170°C (dec.)
Elemental Analysis (%) $C_9H_{13}N_3$
Calculated: C, 66.22; H, 8.03; N, 25.75
Found: C, 65.93; H, 8.00; N, 25.50
NMR (d_6-DMSO) δ: 1.68 (4H, m); 2.38 (2H, t); 2.54 (2H, t); 4.26 (2H, s, NH); 4.97 (2H, s, NH); 7.47 (1H, s)

The reaction is effected in the same manner as above to give Compounds (II1b) (II1c) and (II1d).
(II1b): mp. 196 to 200°C (dec.)
Elemental Analysis $C_8H_{11}N_3O \cdot H_2O$
Calculated: C, 52.45; H, 7.15; N, 22.94
Found: C, 52.18; H, 7.08; N, 22.71
NMR ($CDCl_3$) δ: 2.88 (2H, t); 3.05 (2H, br.s); 3.84 (2H, s); 4.00 (2H, t); 4.63 (2H, s); 7.87 (1H, s)
(II1c): mp. 167 to 168°C
Elemental Analysis (%) $C_{10}H_{15}N_3$
Calculated: C, 67.76; H, 8.53; N, 23.71
Found: C, 67.76; H, 8.48; N, 23.47
NMR (d_6-DMSO) δ: 1.48 to 1.74 (6H, m); 2.58 (2H, m); 2.70 (2H, m); 4.26 (2H, s, NH); 5.02 (2H, s, NH); 7.36 (1H, s)
(II1d): mp. 190 to 193°C
Elemental Analysis (%) $C_8H_{11}N_3$
Calculated: C, 64.40; H, 7.43; N, 28.17
Found: C, 64.43; H, 7.37; N, 28.02
NMR (d_6-DMSO) δ: 1.94 (2H, m); 2.61 (2H, t); 2.63 (2H, t); 4.26 (2H, s, NH); 5.08 (2H, s, NH); 7.43 (1H, s)

Reference Example 2

Preparation of 4-amino-3-(3-isoxazolyl)amino-7,8-dihydro-5H-pyrano[4,3-b]pyridine (II2b)

(1) 3-(3-Isoxazolyl)amino-7,8-dihydro-5H-pyrano[4,3-b]-pyridine-1-oxide 5

To a solution of 2.00 g of 3-nitro-7,8-dihydro-5H-pyrano[4,3-b]pyridine [prepared according to the method as described in Bull. Chem. Soc. Jpn. Vol. 63 (1990), 2820] in 40 ml of methylene chloride is added 2.63 g of m-chloroperbenzoic acid, and the resultant mixture is stirred overnight. The reaction mixture is washed with aqueous potassium carbonate, dried over anhydrous magnesium sulfate and the solvent is evaporated. The crude product is recrystallized from ethanol-chloroform to give 1.82 g of 3-nitro-7,8-dihydro-5H-pyrano[4,3-b]pyridine-1-oxide as colorless crystals. Yield: 84%. To a solution of 1.47 g of the product in 75 ml of methanol-dimethylformamide (1 : 1) is added 100 mg of 10% palladium carbon, and the resultant mixture is hydrogenated at ordinary temperature under atmospheric pressure. After the reduction is completed in about 3 hours, the catalyst is filtered off. The resultant crude crystals are washed with ethanol to give 1.08 g of 3-amino-1-oxide as colorless crystals. Yield: 86%. To a solution of 690 mg of 3-isoxazolylcarbonyl chloride in 20 ml of dimethylformamide is added 414 mg of pyridine under ice cooling, and then 830 mg of 3-amino-1-oxide as crystals is added. The resultant mixture is stirred under ice cooling for 30 minutes and at room temperature for 1 hour, chilled again with ice, and mixed with 4 ml of water. The suspension is neutralized with sodium bicarbonate. The precipitated solid is filtered, washed with water and ethanol in this order and dried to give 1.13 g of the titled compound 5 as colorless crystals.
Yield: 86%.
ml.: 260 to 265°C (dec.)

(2) 3-(3-Isoxazolyl)amino-4-nitro-7,8-dihydro-5H-pyrano-[4,3-b]pyridine-1-oxide 6

A solution of 653 mg of Compound 5 obtained in the above step (1) as crystals in 3.2 ml of fuming nitric acid is stirred at 55°C for 3 hours. The reaction mixture is chilled, poured onto ice water and shaken with chloroform. The extract is washed with water, aqueous disodium hydrogen phosphate and saturated saline in this order, dried over anhydrous magnesium sulfate and concentrated to remove the solvent. The resultant residue is washed with methanol to give 551 mg of the titled compound 6 as light yellow crystals.
Yield: 70%
mp.: 174 to 176°C (dec.)

(3) 3-(3-Isoxazolyl)amino-4-nitro-7,8-dihydro-5H-pyrano-[4,3-b]pyridine 7

To a solution of 473 mg of Compound 6 obtained in the above step (2) in 30 ml of methylene chloride is added a solution of 935 mg of phosphorus tribromide in 1 ml of methylene chloride under ice cooling. The reaction mixture is stirred for 2 hours, mixed with ice water and neutralized with aqueous potassium carbonate under ice cooling. The organic layer is separated, and the aqueous layer is extracted with methylene chloride. The organic layers are combined, washed with saturated saline, dried over anhydrous magnesium sulfate and the solvent is evaporated. The residue is recrystallized from methylene chloride-isopropanol to give 407 mg of the titled compound 7 as yellow crystals.
Yield: 93%
mp.: 143 to 145°C

(4) Preparation of Compound (II2b)

To a solution of 435 mg of Compound 7 obtained in (3) above in 95% aqueous methanol is added 10% palladium carbon (40 mg) as catalyst, and the resultant mixture is hydrogenated at ordinary temperature under atmospheric pressure. The reaction mixture is filtered, and the hardly soluble solid is washed out with dimethylformamide. The filtrate is concentrated in vacuo, and the residue is recrystallized from methanol-methylene chloride to give 280 mg of the titled compound (II2b) as light brown crystals.
Yield: 72%
mp.: 209 to 211°C
Elemental Analysis (%) $C_{12}H_{12}N_4O_3$
Calculated: C, 55.38; H, 4.65; N, 21.53
Found: C, 55.08; H, 4.54; N, 21.24

NMR (d_6-DMSO) δ: 2.73 (2H, t); 3.90 (2H, t); 4.51 (2H, s); 5.93 (2H, s, NH); 7.06 (1H, d); 7.93 (1H, s); 9.15 (1H, d); 10.07 (1H, s, NH)

3-Nitro-6,6-dimethylcyclopenta[b]pyridine is used in the same manner as above to give 4-amino-3-(3-isoxazolylamino)-6,6-dimethylcyclopenta[b]pyridine (II2e).

mp.: 171 to 174°C (dec.)
Elemental Analysis (%) $C_{14}H_{16}N_4O_2$
Calculated: C, 61.75; H, 5.92; N, 20.57
Found: C, 61.41; H, 6.05; N, 20.13
NMR (d_6-DMSO) δ: 1.14 (6H, s); 2.52 (2H, s); 2.61 (2H, s); 5.64 (2H, br.s); 6.99 (1H, d); 7.80 (1H, s); 9.12 (1H, d)

Reference Example 3

Preparation of 3,4-diamino-6-ethoxycarbonyl-5,6,7,8-tetrahydro[1,6]naphthylidine (II1q)

(1) 4-Azido-6-ethoxycarbonyl-5,6,7,8-tetrahydro[1,6]naphthylidine-6-carboxylic acid 8

A mixture of 3 g of ethyl 6-ethoxycarbonyl-4-hydroxy-5,6,7,8-tetrahydro[1,6]naphthylidine-3-carboxylate and 21 ml of phosphorus oxychloride is refluxed under heating for 90 minutes. The reaction mixture is concentrated in vacuo to dryness, and the residue is mixed with ice water and shaken with methylene chloride. The extract is chromatographed on a silica gel column to give oily 4-chloro compound. This compound is dissolved in 70 ml of dimethylformamide, mixed with 1.72 g of sodium amide and stirred at 70°C for 3 hours. After the solvent is evaporated in vacuo, the residue is mixed with water and extracted with chloroform. The extract is chromatographed on a silica gel column to give crystalline 4-azido compound. This compound is dissolved in 30 ml of methanol, mixed with 4N aqueous potasium hydroxide, stirred at room temperature for 1 hour and the methanol is evaporated in vacuo. The residue is made weakly acidic with dilute hydrochloric acid, and the precipitated crystals are filtered and washed to give 1.89 g of 4-azido-3-carboxylic acid 8 as crystals. Yield: 64%
mp.: 171 to 175°C (dec.)

(2) 4-Azido-6-ethoxycarbonyl-3-t-butoxycarbonylamino-5,6,7,8-tetrahydro[1,6]naphthylidine 9

To a solution of 3.4 g of Compound 8 obtained in the above step (1) in 100 ml of tetrahydrofuran is added 1.42 g of triethylamine, and 1.52 g of ethyl chloroformate is dropwise added at -10 to -5°C. After stirring is continued at the same temperature for 1 hour, a solution of 3.81 g of sodium azide in 15 ml of water is dropwise added to the mixture, which is stirred at 0°C for 1 hour. The reaction mixture is concentrated in vacuo, and the residue is mixed with water and shaken with methylene chloride. The extract is dissolved in a mixture of 80 ml of dichloroethane and 40 ml of t-butanol, and the resultant solution is refluxed for 1 hour. The solvent is evaporated, and the residue is chromatographed on a silica gel column to give 3.38 g of 3-t-butoxycarbonylamino compound 9 as crystals.
Yield: 79%
mp.: 144 to 145°C

(3) Preparation of Compound (II1q)

To a solution of 3.30 g of Compound 9 obtained in the above step (2) in 100 ml of tetrahydrofuran/ethanol (1 : 1) is dropwise added a solution of 3.15 g of stannous chloride (II) dihydrate in a mixture of 40 ml of 5N aqueous sodium hydroxide and 50 ml of water at -10°C over a period of 30 minutes, and the resultant mixture is stirred at 0°C for 20 minutes. The solvent is evaporated in vacuo, and the residue is mixed with water and shaken with ethyl acetate. The extract is dissolved in 130 ml of methylene chloride, mixed with 26 ml of trifluoroacetic acid, and stirred at room temperature for 1 hour. The reaction is concentrated in vacuo, and the residue is mixed with saturated saline and neutralized with 5N aqueous sodium hydroxide. The precipitated crystals are filtered, dissolved in methanol, and the resultant solution is concentrated to give 1.98 g of the titled compound (II1g) as crystals. Yield: 90%
mp.: 171 to 174°C (dec.)
Elemental Analysis (%) $C_{11}H_{16}N_4O_2$
Calculated: C, 55.91; H, 6.82; N, 23.71
Found: C, 55.68; H, 6.59; N, 23.79

NMR ($CDCl_3$) δ: 1.31 (3H, t); 2.87 (2H, t); 3.05 (2H, s, NH); 3.75 (2H, t); 3.99 (2H, s, NH); 4.21 (2H, q); 4.42 (2H, s); 7.86 (1H, s)

Ethyl 4-hydroxy-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carboxylate and 4-hydroxy-7,8-dihydro-5H-thiopyrano[4,3-b]pyridine-3-carboxylate are reacted in the same manner as in the above steps (1) to (3) to give Compounds (II1b) and (II1f), respectively.

(II1b): The same physico-chemical data were obtained as in the compound (II1b) prepared in Reference Example 1.

(II1f): mp.: 66 to 67°C

NMR ($CDCl_3$) δ: 2.90 (2H, t); 3.06 (2H, s, NH); 3.13 (2H, t); 3.57 (2H, s); 4.03 (2H, s, NH); 7.85 (1H, s)

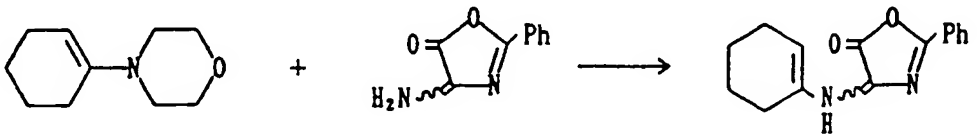
Reference Example 4

Alternative Synthetic Method of (II1b)

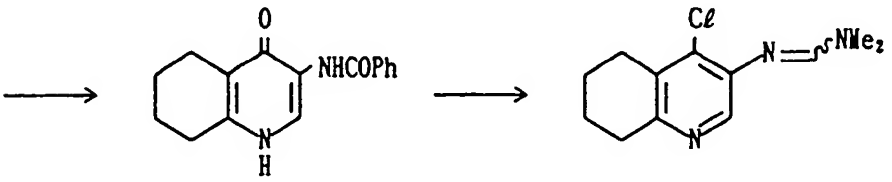
To a solution of 1.50 g of 3-amino-7,8-dihydro-5H-pyrano[4,3-b]pyridine in 45 ml of methylene chloride is added 1.55 ml of trifluoroacetic anhydride with ice cooling and under stirring, and the resultant mixture is stirred at the same temperature for 15 minutes. The reaction mixture is mixed with ice water, made weakly alkaline with aqueous ammonia and extracted with methylene chloride. The extract is washed with saturated saline and the solvent is evaporated. The resultant crude crystals are recrystallized from acetone-isopropyl ether to give 2.14 g of 3-trifluoroacetylamino-7,8-dihydro-5H-pyrano[4,3-b]pyridine as crystals. Yield: 87%. The product (1.55 g) is dissolved in 30 ml of methylene chloride, and 1.63 g of 80% m-chloroperbenzoic acid is added to the solution, which is stirred at room temperature for 2.5 hours. The reaction mixture is mixed with 50 ml of ether, and the precipitated crystals are filtered to give 1.58 g of 3-trifluoroacetylamino-7,8-dihydro-5H-pyrano[4,3-b]pyridine-1-oxide as crystals. Yield: 96%. The product (1.568 g) is mixed with 9.4 ml of fuming nitric acid (d = 1.52) and stirred at 55°C for 6 hours. The reaction mixture is concentrated in vacuo, made alkaline with aqueous ammonia, allowed to stand at room temperature overnight and shaken with 10% methanol/ chloroform. The resultant crude crystals are recrystallized from acetone to give 0.85 g of 3-amino-4-nitro-7,8-dihydro-5H-pyrano[4,3-b]pyridine-1-oxide (II1b) as brown crystals. Yield: 67%. Melting point and spectra data confirmed that the product is the same as the compound (II1b) obtained in Reference Example 1.

Reference Example 5

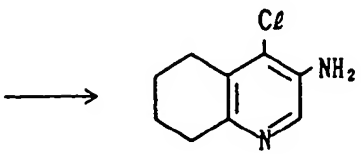
Preparation of 3-amino-4-chloro-5,6,7,8-tetrahydroquinoline (III1a)



(10)



(11) (12)



(III 1 a)

(1) 4-(Cyclohexene-1-ylaminomethylene)-2-phenyl-5(4H)-oxazolone(10)

To 58.5 g of acetic anhydride are added 36.8 g of 1-morpholino-1-cyclohexene and 36 g of 4-aminomethylene-2-phenyl-5(4H)-oxazolone, and the resultant mixture is heated at about 65°C (bath temperature) for 1.5 hours. The reaction mixture is allowed to cool to room temperature, mixed with 90 ml of isopropyl ether and chilled with ice. The precipitated crystals are filtered to give 39.8 g of Compound (10) as yellow crystals melting at 155 to 157°C (dec.). Yield: 78%. The crystals can be used for the subsequent reaction without purification, but a small portion is recrystallized from isopropanol/isopropyl ether to give yellow crystals (10) melting at 156 to 158°C (dec.).

Elemental Analysis (%) $C_{16}H_{16}N_2O_2$
Calculated: C, 71.62; H, 6.01; N, 10.44
Found: C, 71.34; H, 6.05; N, 10.30
NMR ($CDCl_3$) δ: 1.71 (4H, m), 2.18 (4H, m), 5.45 (1H, m), 7.26 to 7.49 (3H, m), 7.67 (1H, d, J=14.0Hz), 7.92 to 8.03 (2H, m), 9.05 (1H, d, J=14.0Hz, NH)

(2) 3-Benzoylamino-5,6,7,8-tetrahydroquinoline-4(1H)-one(11)

A mixture of 36.8 g of Compound (10) and 55 ml of N-methyl-2-pyrrolidone is stirred with heating at 205°C (bath temperature) for 30 minutes. After allowing to cool, the reaction mixture is mixed with acetone and chilled with ice. The precipitated crystals are filtered to give 33.6 g of Compound (11). Yield: 91%. This product can be used for the subsequent reaction without purification, but a small portion is recrystallized from chloroform/methanol to give colorless crystals melting at 408 to 410°C.
Elemental Analysis (%) $C_{16}H_{16}N_2O_2$
Calculated: C, 71.62; H, 6.01; N, 10.44
Found: C, 71.58; H, 6.01; N, 10.49
NMR (d_6-DMSO) δ: 1.45 (2H, m), 1.60 to 1.65 (2H, m), 1.79 (2H, m), 2.73 to 2.78 (4H, m), 7.52 to 7.63 (3H, m), 7.87 to 7.92 (2H, m), 8.55 (1H, d, J=6.0Hz), 9.39 (1H, s, NH), 11.44 (1H, br d, NH)

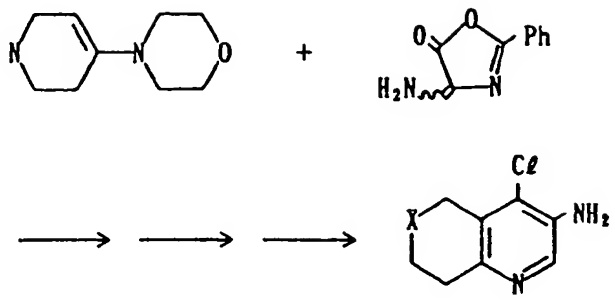
(3) 4-Chloro-3-(N,N-dimethylaminomethyleneamino)-5,6,7,8-tetrahydroquinoline(12)

To a suspension of 5.36 g of Compound (11) in 26 ml of dimethylformamide is dropwise added a solution of 2.8 ml of phosphorus oxychloride in 8 ml of dimethylformamide at temperature from -10 to -5°C, and the temperature is gradually raised up to room temperature. The reaction mixture is stirred overnight, chilled with ice, poured onto ice water and extracted with methylene chloride to remove the acidic and neutral by-products. The aqueous layer is made alkaline with conc. aqueous ammonia under ice cooling and shaken with ethyl acetate. The extract is washed with saturated saline, dried and concentrated in vacuo. The residue is chromatographed on an alumina column, eluting with methylene chloride/acetonitrile (40 : 1) to give 3.73 g of Compound (12) as colorless crystals melting at 62 to 64°C. Yield: 79%.
Elemental Analysis (%) $C_{12}H_{16}N_3Cl$
Calculated: C, 60.62; H, 6.79; N, 17.68; Cl, 14.92
Found: C, 60.70; H, 6.83; N, 17.75; Cl, 14.77
NMR ($CDCl_3$) δ: 1.79 to 1.87 (4H, m), 2.77 to 2.88 (4H, m), 3.06 (6H, s), 7.45 (1H, s), 7.90 (1H, s)

(4) 3-Amino-4-chloro-5,6,7,8-tetrahydroquinoline(III1a)

A solution of 3.60 g of Compound (12) in 25 ml of 3N sulfuric acid is stirred at 100°C (bath temperature) for 1.5 hours. The reaction mixture is made alkaline with aqueous ammonia, mixed with saline and extracted with methylene chloride. The extract is dried and concentrated to give 2.61 g of Compound (III1a) as colorless crystals melting at 114 to 117°C (dec.). Yield: 94%. The crystals can be used for the subsequent reaction without purification, but a small portion is recrystallized from methylene chloride/isopropyl ether to give colorless crystals melting at 115 to 117°C (dec.).
Elemental Analysis (%) $C_9H_{11}N_2Cl$
Calculated: C, 59.18; H, 6.07; N, 15.34; Cl, 19.41
Found: C, 59.05; H, 6.03; N, 15.30; Cl, 19.32
NMR ($CDCl_3$) δ: 1.78 to 1.87 (4H, m), 2.72 to 2.85 (4H, m), 3.91 (2H, br s, NH 2), 7.96 (1H, s)

Reference Examples 6 to 8



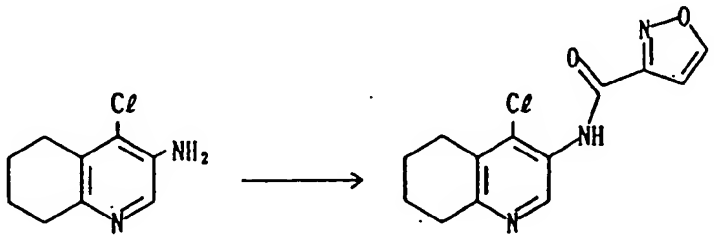
(Ⅲ 1)

Using the corresponding enamines, the reaction is effected in the same manner as in Reference Example 5 to give the following compounds.

IIIlb (X = O): (Reference Example 6)
mp.: 125 to 127°C
Elemental Analysis (%) $C_8H_9N_2OCl$
Calculated: C, 52.04; H, 4.91; N, 15.18; Cl, 19.20
Found: C, 52.08; H, 4.88; N, 15.12; Cl, 19.44
NMR ($CDCl_3$) δ: 2.91 (2H, t, J=5.8Hz), 4.00 (2H, t, J=5.8Hz), 4.00 (2H, br s, NH2), 4.75 (2H, AB-q), 8.05 (1H, s)
IIIlc (X = $-CH_2CH_2-$): (Reference Example 7)
mp.: 144 to 146°C
Elemental Analysis (%) $C_{10}H_{13}N_2Cl$
Calculated: C, 61.06; H, 6.66; N, 14.24; Cl, 18.02
Found: C, 61.06; H, 6.63; N, 14.25; Cl, 18.14
NMR ($CDCl_3$) δ: 1.60 to 1.72 (4H, m), 1.79 to 1.88 (2H, m), 2.94 to 2.99 (4H, m), 3.94 (2H, br s, NH2), 7.84 (1H, s)
IIIlf (X = S): (Reference Example 8)
mp.: 129 to 132°C
Elemental Analysis (%) $C_8H_9N_2SCl$
Calculated: C, 47.87; H, 4.51; N, 13.95; S, 15.97; Cl, 17.66
Found: C, 47.79; H, 4.52; N, 13.93; S, 16.10; Cl, 17.52
NMR ($CDCl_3$) δ: 2.92 (2H, t, J=6.2Hz), 3.15 (2H, t, J=6.2Hz), 3.84 (2H, s), 4.00 (2H, br s, NH2), 8.02 (1H, s)

Reference Example 9

Preparation of 4-chloro-3-(isoxazole-3-carbonylamino)-5,6,7,8-tetrahydroquinoline (III2a-1)



(Ⅲ 1 a) (Ⅲ 2 a - 1)

To a solution of 4.20 g of 3-amino-4-chloro-5,6,7,8-tetrahydroquinoline (IIIla) and 1.96 g of pyridine in 80 ml of methylene chloride is added a solution of 3.24 g of isoxazole-3-carbonyl chloride in 4 ml of methylene

chloride, and the resultant mixture is stirred at room temperature for 2 hours. The reaction mixture is mixed with ice water, adjusted to pH 10 with conc. aqueous ammonia to pH 10, and stirred at room temperature for 10 minutes. The organic layer is separated, and the aqueous layer is extracted with methylene chloride. The combined extracts are washed with water, dried and the solvent is evaporated to give 5.9 g of Compound (III2a-1) as crystals melting at 150 to 153°C (dec.). Yield is 92%. The crystals can be used for the subsequent reaction without purification, but a small portion is recrystallized from isopropyl ether/methylene chloride to give colorless crystals melting at 151 to 153°C (dec.).

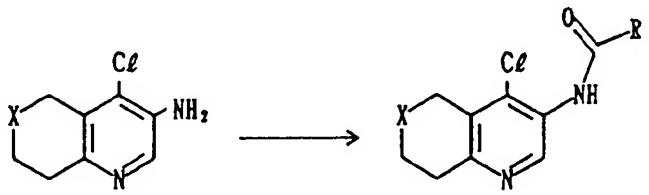
Elemental Analysis (%) $C_{13}H_{12}N_3O_2Cl$

Calculated: C, 56.22; H, 4.35; N, 15.13; Cl, 12.76

Found: C, 56.12; H, 4.41; N, 15.26; Cl, 12.91

NMR ($CDCl_3$) δ: 1.85 to 1.91 (4H, m), 2.78 to 2.85 (2H, m), 2.92 to 2.98 (2H, m), 6.94 (1H, d, J=1.6 Hz), 8.56 (1H, d, J=1.6Hz), 8.96 (1H, br s, NH), 9.38 (1H, s)

Reference Examples 10 to 14



(Ⅲ1) (Ⅲ2)

Using the corresponding pyridine derivatives (III1a), (III1b), (III1c) and (III1f), the reaction is effected as in Reference Example 9 to give the following compounds.

III2a-2 (X = CH_2 ; R = 3-methyl-5-isoxazolyl): (Reference Example 10)

mp.: 138 to 139°C

Elemental Analysis (%) $C_{14}H_{14}N_3O_2Cl$

Calculated: C, 57.64; H, 4.84; N, 14.40; Cl, 12.15 Found: C, 57.53; H, 4.82; N, 14.46; Cl, 12.37

NMR ($CDCl_3$) δ: 1.88 (4H, m), 2.42 (3H, s), 2.82 (2H, m), 2.95(2H, m), 6.90 (1H, s), 9.35 (1H, s), 9.57 (1H, br s, NH)

III2b-1 (X = 0 ; R = 3-Isoxazolyl): (Reference Example 11)

mp.: 180 to 181°c

Elemental Analysis (%) $C_{12}H_{10}N_3O_3Cl$

Calculated: C, 51.53, H, 3.60; N, 15.02; Cl, 12.68

Found: C, 51.60; H, 3.60; N, 14.97; Cl, 12.93

NMR ($CDCl_3$) δ: 3.04 (2H, t, J=5.8Hz), 4.06 (2H, t, J=5.8Hz), 4.81 (2H, AB-q), 6.95 (1H, d, J=1.8Hz), 8.57 (1H, d, J=1.8Hz), 8.94 (1H, br s, NH), 9.47 (1H, s)

III2c-1 (X = $-CH_2CH_2-$; R = 3-isoxazolyl): (Reference Example 12)

mp.: 115 to 116°C

Elemental Analysis (%) $C_{14}H_{14}N_3O_2Cl$

Calculated: C, 57.63; H, 4.83; N, 14.40; Cl, 12.15

Found: C, 57.93; H, 4.98; N, 14.38; Cl, 11.89

NMR ($CDCl_3$) δ: 1.63 to 1.76 (4H, m), 1.71 to 1.92 (2H, m), 3.03 to 3.13 (4H, m), 6.94 (1H, d, J=1.8Hz), 8.56 (1H, d, J=1.8Hz), 9.00 (1H, br s, NH), 9.31 (1H, s)

III2f-1 (X = S ; R = 3-isoxazolyl): (Reference Example 13)

mp.: 155 to 156°C

Elemental Analysis (%) $C_{12}H_{10}N_3O_2SCl$

Calculated: C, 48.73; H, 3.40; N, 14.20; S, 10.84; Cl, 11.98

Found: C, 48.58; H, 3.48; N, 14.22; S, 10.75; Cl, 11.99

NMR ($CDCl_3$) δ: 2.98 (2H, t, J=5.8Hz), 3.29 (2H, t, J=5.8Hz), 3.90 (2H, s), 6.95 (1H, d, J=1.8Hz), 8.57 (1H, d, J=1.8Hz), 8.98 (1H, br s, NH), 9.47 (1H, s)

III2f-2 (X = S ; R = 3-methyl-5-isoxazolyl): (Reference Example 14)

mp.: 172 to 173°C

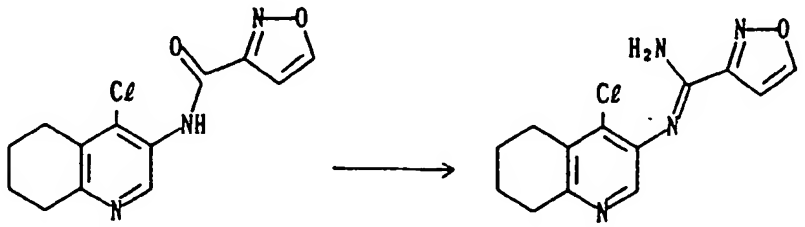
Elemental Analysis (%) $C_{13}H_{12}N_3O_2SCl$

Calculated: C, 50.40; H, 3.90; N, 13.56; S, 10.35; Cl, 11.44

Found: C, 50.58; H, 4.01; N, 13.47; S, 10.35; Cl, 11.52
NMR ($CDCl_3$) δ: 2.42 (3H, s), 2.98 (2H, t, 1=6.6Hz), 3.29 (2H, t, 1=6.6Hz), 3.90 (2H, s), 6.92 (1H, s), 8.58 (1H, br s, NH), 9.44 (1H, s)

Reference Example 15

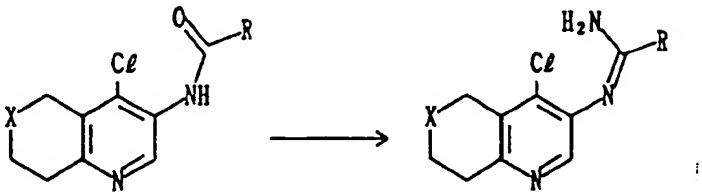
Preparation of 4-chloro-3-(amino(3-isoxazolyl)-methyleneamino)-5,6,7,8-tetrahydroquinoline (III3a-1)



(Ⅲ2a-1) (Ⅲ3a-1)

To 60 ml of methylene chloride are added 5.55 g of Compound (III2a-1) and 6.97 g of phosphorus pentachloride, and 1.60 g of pyridine is dropwise added. The resultant mixture is refluxed for 4.5 hours. To a previously chilled about 3.6N ammonia/isopropanol solution (140 ml) is added the above reaction mixture chilled with ice under keeping at temperature from -30 to -15°C. Temperature is raised up to room temperature, and the mixture is stirred for 18 hours. The solvent is evaporated in vacuo, and the residue is mixed with 50 ml of ice water and 100 ml of methylene chloride and adjusted to pH 10 with conc. aqueous ammonia. The mixture is stirred at room temperature for 15 minutes and the methylene chloride layer is separated. The aqueous layer is further extracted with methylene chloride. The extract is washed with water, dried and concentrated for evaporation of the solvent to give 5.1 g of the titled compound (III3a-1) as crystals melting at 160 to 163°C. Yield: 92%. The crystals can be used for the subsequent reaction without purification, but a small portion is recrystallized from methylene chloride/isopropyl ether to give colorless crystals melting at 162 to 162°C.
Elemental Analysis (%) $C_{13}H_{13}N_4OCl$
Calculated: C, 56.42; H, 4.73; N, 20.24; Cl, 12.81
Found: C, 56.53; H, 4.91; N, 20.27; Cl, 12.72
NMR ($CDCl_3$) δ: 1.83 to 1.92 (4H, m), 2.78 to 2.86 (2H, m), 2.89 to 2.95 (2H, m), 5.38 (2H, br s, NH2), 6.98 (1H, d, J=1.6Hz), 8.07 (1H, s), 8.49 (1H, d, J=1.6Hz)

Reference Examples 16 to 20



(Ⅲ2) (Ⅲ3)

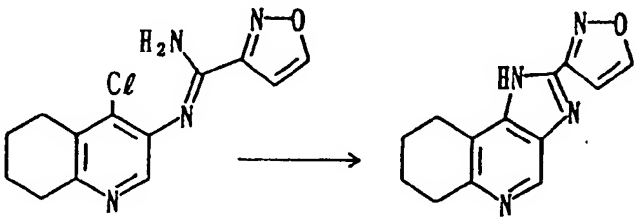
Using the corresponding isoxazolecarbonylamino derivatives (III2a), (III2b), (III2c), (III2f-1) and (III2f-2), the reaction is effected in the same manner as in Reference Example 15, whereby the following compounds are prepared.

III3a-2 (X = CH_2 ; R = 3-methyl-5-isoxazolyl): (Reference Example 16)
mp.: 206 to 208°C
Elemental Analysis (%) $C_{14}H_{15}N_4OCl$
Calculated: C, 57.83; H, 5.20; N, 19.27; Cl, 12.20
Found: C, 57.80; H, 5.22; N, 19.16; Cl, 11.91
NMR ($CDCl_3$) δ: 1.84 (4H, m), 2.38 (3H, s), 2.83 (4H, m), 5.50 (2H, br s, NH2), 6.84 (1H, s), 8.02 (1H, s)
III3b-1 (X = O ; R = 3-isoxazolyl): (Reference Example 17)

mp.: 195 to 196°C
Elemental Analysis (%) $C_{12}H_{11}N_4O_2Cl$
Calculated: C, 51.71; H, 3.98; N, 20.10; Cl, 12.72
Found: C, 51.49; H, 4.03; N, 19.95; Cl, 12.66
NMR ($CDCl_3$) δ: 2.99 (2H, t, J=6.0Hz), 4.04 (2H, t, J=6.0Hz), 4.80 (2H, AB-q), 5.45 (2H, br s, NH2), 6.98 (1H, d, J=1.8Hz), 8.15 (1H, s), 8.50 (1H, d, J=1.8Hz)
III3c-1 (X = $-CH_2CH_2-$; R = 3-isoxazolyl): (Reference Example 18)
mp.: 197 to 199°C
Elemental Analysis (%) $C_{14}H_{15}N_4OCl$
Calculated: C, 57.83; H, 5.19; N, 19.26; Cl, 12.19
Found: C, 57.57; H, 5.28; N, 19.11; Cl, 11.91 NMR ($CDCl_3$) δ: 1.63 to 1.93 (6H, m), 3.04 (3.09 (4H, m)), 5.41 (2H, br s, NH 2), 6.98 (1H, d, J=1.6Hz), 7.96 (1H, s), 8.49 (1H, d, J=1.6Hz)
III3f-1 (X = S ; R = 3-isoxazolyl): (Reference Example 19)
mp.: 190 to 192°C
Elemental Analysis (%) $C_{12}H_{11}N_4OSCl$
Calculated: C, 48.89; H, 3.76; N, 19.00; S, 10.87; Cl, 12.02
Found: C, 48.73; H, 3.75; N, 18.74; S, 10.85; Cl, 12.32
NMR ($CDCl_3$) δ: 2.97 (2H, t, J=6.2Hz), 3.24 (2H, t, J=6.2Hz), 3.92 (2H, s), 5.46 (2H, br s, NH2), 6.98 (1H, d, J=1.8Hz), 8.13 (1H, s), 8.51 (1H, d, J=1.8Hz)
III3f-2 (X = S ; R = 3-methyl-5-isoxazolyl): (Reference Example 20)
mp.: 194 to 196°C
Elemental Analysis (%) $C_{13}H_{13}N_4OSCl$
Calculated: C, 50.56; H, 4.24; N, 18.14
Found: C, 50.63; H, 4.13; N, 18.07
NMR ($CDCl_3$) δ: 2.39 (3H, s), 2.96 (2H, t, J=6.2Hz), 3.22 (2H, t, J=6.2Hz), 3.91 (2H, s), 5.36 (2H, br s, NH2), 6.85 (1H, s), 8.11 (1H, s)

Example 37

2-(3-Isoxazolyl)-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline (Ia-7)

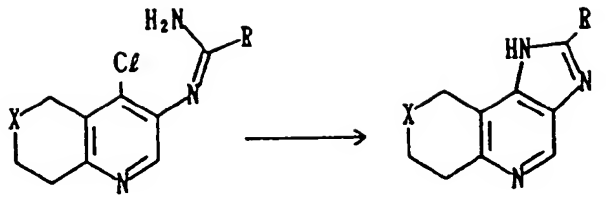


(III 3 a − 1) (I a − 7)

A mixture of 2.00 g of Compound (III3a-1) (obtained in Reference Example 15) and 18 ml of N-methyl-2-pyrrolidone is heated at 205°C (bath temperature) for 1 hour. The solvent is evaporated in vacuo, and the residue is mixed with acetone and chilled. The precipitated crystals are filtered to give 1.83 g of Compound (Ia-7) hydrochloride. Yield: 91%. mp.: 263 to 267°C (dec.). This product is recrystallized from methanol/isopropanol to give colorless crystals melting at 265 to 269°C (dec.).
Elemental Analysis (%) $C_{13}H_{13}N_4OCl \cdot 1/2H_2O$
Calculated: C, 54.65; H, 4.94; N, 19.61; Cl, 12.41
Found: C, 54.64; H, 5.14; N, 19.67; Cl, 12.71

The above hydrochloride is converted into free base in a conventional manner to give the compound identified as Compound (Ia-7) obtained in Example 32.

Examples 38 to 42



(Ⅲ3) (I)

The reaction is effected in the same manner as in Example 37 to give Compound (Ia-6) (Example 38), Compound (Ib-7) (Example 39), Compound (Ic-6) (Example 40) and Compound (If-1) (Example 41) from Compound (III3a-2) (obtained in Reference Example 16), Compound (III3b-1) (obtained in Reference Example 17), Compound (III3c-1) (obtained in Reference Example 18) and Compound (III3f-1) (obtained in Reference Example 19), respectively. Physico-chemical data of these compounds were identical with those of the compounds obtained in Examples 16, 25, 19 and 31, respectively.

Further, the reaction is effected in the same manner as in Example 37 to give 2-(3-methyl-5-isoxazolyl)-1,6,7,9-tetrahydroimidazo [4,5-d]thiopyrano[4,3-b]pyridine hydrochloride (If-2) (X = S ; R = 3-methyl-5-isoxazolyl, Example 42) from Compound (III3f-2) (obtained in Reference Example 20).

mp.: 244 to 246°C (dec.)

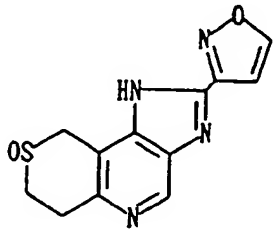
Elemental Analysis (%) $C_{13}H_{13}N_4OSCl$

Calculated: C, 50.56; H, 4.24; N, 18.14; S, 10.38; Cl, 11.48

Found: C, 50.39; H, 4.35 ; N, 17.85; S, 10.33; Cl, 11.37 NMR (d_6-DMSO) δ: 2.41 (3H, s), 3.12 (2H, t, J=5.6Hz), 3.38 (2H, t, J=5.6Hz), 4.25 (2H, s), 7.48 (1H, s), 9.35 (1H, s)

Example 43

2-(3-Isoxazolyl)-8-oxo-1,6,7,9-tetrahydroimidazo[4,5-d]thiopyrano[4,3-b]pyridine (If-3)



(I f - 3)

To a solution of 323 mg of Compound (If-1) in 30 ml of methanol is added a solution of 289 mg of sodium metaperiodate in 3 ml of water, and the resultant mixture is stirred at room temperature for 4 hours. The crystals in the reaction mixture are filtered off, and the filtrate is concentrated in vacuo. The residue is chromatographed on an alumina column, eluting with chloroform/methanol (15 : 1) to give 326 mg of Compound (If-3) as colorless crystals. Yield: 95%. The crystals are recrystallized from ethyl acetate/methanol to give Compound (If-3) as crystals melting at 210 to 212°C (dec.)

Elemental Analysis (%) $C_{12}H_{10}N_4O_2S$

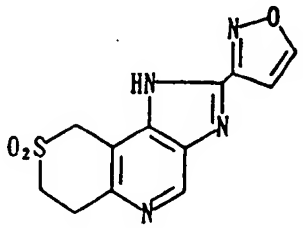
Calculated: C, 52.54; H, 3.67; N, 20.42; S, 11.68

Found: C, 52.45; H, 3.90; N, 20.18; S, 11.43

NMR (d_6-DMSO) δ: 3.16 to 3.42 (4H, m), 4.38 (2H, AB-q), 7.26 (1H, d, J=1.6Hz, 8.87 (1H, s), 9.23 (1H, d, J=1.6Hz)

Example 44

2-(3-Isoxazolyl)-8,8-dioxo-1,6,7,9-tetrahydroimidazo-[4,5-d]thiopyrano[4,3-b]pyridine hydrochloride (If-4)



(I f − 4)

To a solution of 592 mg of Compound (III2f-1) (obtained in Reference Example 13) in 35 ml of methylene chloride is added 1.42 g of m-chloroperbenzoic acid under ice cooling, and the resultant mixture is stirred at room temperature for 6 hours. The reaction mixture is concentrated in vacuo, and the crystalline residue is washed well with isopropyl ether to give 670 mg of 4-chloro-3-(isoxazole-3-carbonylamino)-1,6,6-trioxo-7,8-dihydro-5H-thiopyrano[4,3-b]pyridine as crystals melting at 218 to 220°C (dec.). Yield: 98%.

To a solution of 460 mg of the crystals in 92 ml of methylene chloride is dropwise added a solution of 0.26 ml of phosphorus tribromide in 0.3 ml of methylene chloride at temperature from -10 to -5°C, and the resultant mixture is stirred at temperature from 0 to 5°C for 5 hours. The reaction mixture is mixed with ice water, neutralized with potassium carbonate and shaken with chloroform. The extract is dried and concentrated to remove the solvent. The residue is chromatographed on an alumina column, eluting with methylene chloride/isopropyl ether (30 : 1) to give 330 mg of 4-chloro-3-(isoxazolyl-3-carbonylamino)-6,6-dioxo-7,8-dihydro-5H-thiopyrano[4,3-b]pyridine as crystals melting at 200 to 202°C. Yield: 75%.

Using this compound, the reaction is effected in the same manner as in the method used for converting Compound (III2a-1) (obtained in Reference 9) into Compound (Ia-7), whereby Compound (If-4) is obtained.

mp.: 199 to 202°C

Elemental Analysis (%) $C_{12}H_{11}N_4O_3SCl \cdot H_2O$

Calculated: C, 41.80; H, 3.80; N, 16.25; S, 9.29; Cl, 10.28

Found: C, 41.53; H, 3.74; N, 16.16; S. 9.12; Cl, 9.99 NMR (d_6-DMSO) δ: 3.73 (4H, s), 4.93 (2H, s), 7.40 (1H, d, J=1.6Hz), 9.33 (1H, d, J=1.6Hz), 9.38 (1H, s).

The compounds of the present invention show high affinity to cerebral benzodiazepine receptor, and are useful for treating various psychotropic disorders. The study of various drugs having an ability of binding to this receptor has revealed that these drugs can be classified in the following five groups according to their functions (aggressive or suppressive) and their potency (strong or weak) in the central nervous system: 1) Full agonist (central nerve inhibition, antianxiety, anticonvulsion), 2) partial agonist (selective antianxiety), 3) antagonist (antagonism to both aggressive and suppressive actions), 4) partial inverse agonist (central nervous acceleration, convulsion or recognition reinforcing activity, anaesthesia antagonism), 5) full inverse agonist (induction of convulsion or anxiety). Further, it is also known that to which group a particular drug belongs can be determined by measuring the strength of inhibitory or reinforcing activity on the convulsion induced by the administration of pentylenetetrazole [C, Braestrup et al., Biochem. Pharmacol. 33, 859 (1984)]. It is pointed out by M. Sarter et al., TINS 11, 13 (1988), that a partial inverse agonist can be nootropic agent or cognition enhancer, in view of the fact that methyl β-carboline-3-carboxylic acid (β-CCM), a kind of inverse agonist, can reinforce the memorial and learning behavior of an animal, or that diazepam, a kind of agonist, inhibits human memory. Accordingly, of the compounds of the present invention, those showing agonist activity are expected to be useful as antianxiety agents or anti convulsants, those showing antagonistic activity are expected to be useful as antagonists against overdosage of benzodiazepines, and those showing inverse agonist activity are expected to be useful as psychotropic agents, nootropic agents or anaesthesia antagonists.

The compounds of the present invention were subjected to the following pharmacological experiments. The numbers of the test compounds listed in the tables correspond to those used in the foregoing Examples.

Experiment 1

Test on Binding to Benzodiazepine Receptor

This test was carried out modifying partially a method of Moehler & Okada, Science, 198, 849-851 (1977). Receptor preparation was provided from the cerebral cortex of male Wistar rats (11-13 weeks age). Inhibitory action of the test compound on the specific binding of tritium-labelled diazepam to the receptor was evaluated as follows: 2nM tritium-labelled diazepam and an aqueous solution of the test compound in 5 or 6 different concentrations were incubated with the receptor preparation at 0°C for 60 minutes. The 50% inhibitory concentration (IC_{50}) was measured by the concentration-response curve. In addition, the inhibitory constant (Ki) of the test compound was calculated by dissociation constant (Kd) and concentration (L) of tritium-labelled diazepam. Table 1 shows the experimental results.

$$Ki = IC_{50} \div (1 + L/Kd)$$

Table 1

Test Compound	Ki (nM)
Ia-1	13.7
Ia-3	1.90
Ia-5	3.46
Ia-6	2.19
Ia-7	1.30
Ib-5	6.97
Ib-7	2.09
Ic-3	6.06
Ic-6	2.29
Ic-7	9.47
Id-1	2.55
Id-2	8.94
Ie-1	7.20
If-1	0.44
Ig-1	2.80

Experiment 2

Antagonism of Pentylenetetrazole-Induced Convulsion

Agonistic activity was evaluated in this Experiment. Pentylenetetrazole was subcutaneously administered male mice (a group of 8-16 male mice was employed in each test) at a dose of 125 mg/kg immediately after intravenous injection of the test compound. The dose (ED_{50}) required to prevent tonic convulsion and death in 50% of the animals during subsequent 2-hour observation period was calculated by the probit method. Table 2 shows the experimental results.

Table 2

Test Compound	ED_{50} (mg/kg)
Ia-1	7.85
Ia-6	0.17
Ib-5	0.80
Ic-7	1.05
Id-2	0.74
Ig-1	3.69

Experiment 3

Potentiation of Pentylenetetrazole-Induced Convulsion

Inverse agonist activity was evaluated in this Experiment. Pentylenetetrazole was subcutaneously administered to male mice (a group of 8-16 male mice was employed in each test) at a dose of 90 mg/kg immediately after intravenous injection of the test compound. The dose (ED_{50}) required to produce tonic convulsion and death in 50% of the animals during the subsequent 2-hour observation period was calculated by the probit method. Table 3 shows the experimental results.

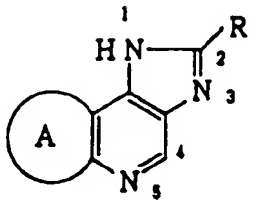
Table 3

Test Compound	ED_{50} (mg/kg)
Ib-7	1.27
Id-1	0.40
Id-1	0.25
If-1	0.96

As shown above, the compounds of the present invention show high affinity to benzodiazepine receptor and exhibit inhibitory or accelerating activity to the central nervous system.

Claims

1. A compound of the formula (I):



(I)

wherein R represents an optionally substituted aryl group or an optionally substituted aromatic heterocyclic group; ring A represents a 5 to 9 membered alicyclic group, in which one or more carbon atoms constituting said ring A may be replaced by O, S, SO, SO_2 and/or NR^1 (in which R^1 means hydrogen, alkyl, alkoxycarbonyl, carbamoyl or an acyl group) and/or said ring A may have an alkyl group as a substituent, or its salt.

2. A compound as claimed in Claim 1 wherein R represents optionally substituted isoxazolyl.

3. A compound as claimed in Claim 1 or Claim 2 wherein the ring A is a dihydrothiopyrano, cyclohexeno, or dihydropyrano ring.

4. A compound as claimed in Claim 1, which is 2-(3-isoxazolyl)-1,6,7,9-tetrahydroimidazo[4,5-d]pyrano-[4,3-b]pyridine or its salt.

5. A pharmaceutical composition comprising a compound as claimed in any one of the preceding claims together with a carrier or excipient therefor.

6. A pharmaceutical composition as claimed in Claim 5 for use in the treatment of a psychotropic disorder.

7. A pharmaceutical composition as claimed in Claim 5 for use as an antianxiety agent.

8. A pharmaceutical composition as claimed in Claim 5 for use as an anaesthesia antagonistic agent.

9. A pharmaceutical composition as claimed in Claim 5 for use as a cerebral function activator.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 30 0901

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A,D	EP-A-0 223 420 (SHIONOGI) * page 49, line 35 - line 45; claim 1 * & JP-A-6 399 069 (SHIONOGI) ---	1,5	C07D471/04 C07D491/147 C07D471/14 C07D495/14 A61K31/435 //(C07D471/04, 235:00,221:00) (C07D491/147, 311:00,235:00, 221:00) (C07D471/14, 235:00,221:00, 221:00) (C07D495/14, 335:00,235:00, 221:00)
A,D	EP-A-0 168 350 (CIBA-GEIGY) * claims 1,32 * & US-A-4 740 512 -----	1,5	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07D
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	29 APRIL 1993	ALFARO FAUS I.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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L : document cited for other reasons

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